

Reimbursement Recommendation

Tofersen (Qalsody)

Indication: For the treatment of adults with amyotrophic lateral sclerosis associated with a mutation in the superoxide dismutase 1 gene

Sponsor: Biogen Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Qalsody?

Canada's Drug Agency (CDA-AMC) recommends that Qalsody be reimbursed by public drug plans for the treatment of adults with amyotrophic lateral sclerosis (ALS) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Qalsody should only be covered for adults (aged 18 years or older) who have ALS associated with a confirmed *SOD1* gene mutation, verified through genetic testing, and who exhibit muscle weakness attributable to ALS.

What Are the Conditions for Reimbursement?

Qalsody should only be reimbursed when it is prescribed and monitored by an ALS specialist such as a neurologist or physiatrist within a multidisciplinary clinic, and the cost of Qalsody is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that in the first 28 weeks, Qalsody did not show a clear difference compared to placebo. However, in a longer follow-up study, the health of patients who received Qalsody earlier seemed to decline more slowly and they had better breathing compared to those who received Qalsody later. These results suggest Qalsody may help, but the overall benefit is still uncertain.
- Patients living with ALS and their caregivers want treatments that slow disease progression, help maintain independence, improve health-related quality of life (HRQoL), and extend survival. Qalsody showed signs of slowing down loss of function related to ALS.
- Based on the CDA-AMC assessment of the health economic evidence, Qalsody does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Qalsody is estimated to cost the public drug plans approximately \$36 million over the next 3 years. The actual budget impact of reimbursing Qalsody will depend on number of people eligible for treatment.

Additional Information

What Is ALS?

ALS is a rare disease that affects the nerve cells that control muscles, which causes muscle weakness, loss of independence, and, usually,

Summary

breathing problems. ALS gets worse over time and is usually life-threatening within 3 to 5 years after diagnosis. *SOD1* ALS is an ultrarare genetic subtype caused by mutations in the *SOD1* gene. In Canada, about 40 people have this form, while ALS overall affects about 7 out of every 100,000 people.

Unmet Needs in ALS

Currently available treatments can slow ALS disease progression a little or help some people live longer, but they do not address the root cause or stop the disease from progressing. New treatments that can slow ALS more effectively, help people keep their strength and independence, improve survival, and target the genetic changes that cause ALS are needed.

How Much Does Qalsody Cost?

Treatment with Qalsody is expected to cost approximately \$425,560 per patient in the first year of treatment and \$368,819 per patient in subsequent years, based on the Health Canada–recommended loading and maintenance dosages.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that tofersen be reimbursed for the treatment of adults with ALS associated with a mutation in the *SOD1* gene only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

ALS is a rare, progressive neurodegenerative disease characterized by the loss of motor neurons that leads to progressive muscle weakness, loss of function, and, typically, death from respiratory failure within 3 to 5 years of diagnosis. *SOD1* ALS is an ultrarare genetic subtype caused by mutations in the *SOD1* gene. The patient groups emphasized that there is a need for effective therapies for patients with *SOD1* ALS that slow progression, preserve physical function and independence, extend survival, and improve HRQoL. They also emphasized that both median survival and disease duration in the *SOD1* ALS population are significantly shorter than the broader ALS patient population.

One pivotal randomized, double-blind, placebo-controlled trial (VALOR; N = 108 over 28 weeks, with 72 participants included in the primary analysis) and its open-label extension to 104 weeks, which evaluated the efficacy of tofersen in patients receiving background care, suggested that tofersen may result in added clinical benefit of undetermined clinical significance. The primary end point change in Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score at 28 weeks did not demonstrate a statistically significant difference versus placebo. Although the extension phase was uncontrolled and subject to several limitations, it suggested a potential clinical benefit with earlier initiation of tofersen, including a slower rate of functional decline (ALSFRS-R score difference of 3.5 points at 52 weeks) and improved respiratory function (slow vital capacity [SVC] improvement of 9.2% predicted at 52 weeks) compared to delayed treatment.

Patients and caregivers cited the urgent need for therapies that slow progression, preserve function and independence, extend survival, and improve HRQoL. Across the VALOR trial, its extension, and real-world cohorts, tofersen met some of these needs by demonstrating a numerically slower loss of functional ability. However, these numerical results are associated with a high level of uncertainty due to failure to meet prespecified end points and the nature of the uncontrolled extension and cohort studies.

Using the sponsor-submitted price for tofersen and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for tofersen plus background therapy was \$1,586,423 per quality-adjusted life-year (QALY) compared with background therapy alone. At this ICER, tofersen plus background therapy is not cost-effective at a \$50,000 per QALY gained willingness-to-pay threshold for patients with *SOD1* ALS. CDA-AMC notes that the results of the analysis are driven by the predicted improvement in life expectancy associated with tofersen, which results in additional drug acquisition costs for background therapy, as well as nondrug-related costs. A price reduction is required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Tofersen can be initiated in those with <i>SOD1</i> ALS with all of the following: 1.1. are 18 years of age or older 1.2. have weakness attributable to ALS and a documented mutation in the <i>SOD1</i> gene.	The VALOR trial provided evidence of safety and efficacy for the use of tofersen in adults with weakness attributable to ALS and a documented mutation in the <i>SOD1</i> gene.	—
Discontinuation		
2. Reimbursement of tofersen should be discontinued if 1 of the following conditions are met: 2.1. permanent ventilation, defined as invasive or noninvasive ventilation of ≥ 22 hours per day for ≥ 21 consecutive days 2.2. formal transition to comfort-focused care (patient or caregiver decision).	These criteria mark points at which the expected benefit–risk or benefit–burden balance of tofersen becomes unfavourable, as agreed by ALS specialists in Canada and reflected in the VALOR trial. The event of permanent ventilation was part of the end points used in the VALOR trial to assess the efficacy of tofersen, where the occurrence of the event indicated important disease progression. Transition to comfort-focused care reflects patient-centred care: when goals shift solely to comfort, the procedural risk and travel demands of tofersen outweigh any incremental preservation of function. The clinical experts noted that reaching a very advanced, end-stage disease state with minimal remaining neurologic function, where the potential for benefit is considered negligible compared to the treatment burden, often leads to discontinuation. The need for permanent ventilation (either via tracheostomy or 24/7 noninvasive support) frequently prompts discussions about end-of-life care and treatment discontinuation.	CDEC noted that the initiation of continuous ventilatory support is a clinical marker of end-stage disease and typically signals the need for a comfort-focused approach to care. This transition has important implications for patient management, including a shift in therapeutic goals toward comfort and quality of life. CDEC also emphasized the need for drug plans to establish a clear mechanism to adjudicate such cases, ensuring appropriate access to therapies while aligning with clinical intent and resource stewardship.
Prescribing		
3. Tofersen must be prescribed and its use overseen by an ALS specialist neurologist or physiatrist in a multidisciplinary clinic and lumbar puncture administration must be performed by a clinician trained in intrathecal delivery.	The trial sites were tertiary ALS centres; expert consensus stresses specialist oversight for patient selection, adverse events management (e.g., intracranial pressure), and coordination of monthly intrathecal dosing.	Jurisdictions may designate ALS centres for oversight; intrathecal dosing can be delegated to local proceduralists under a written protocol approved by the centre.

Reimbursement condition	Reason	Implementation guidance
Pricing		
4. A reduction in price	The ICER for tofersen plus background therapy is \$1,586,423 per QALY gained when compared with background therapy alone. Tofersen's cost-effectiveness is highly uncertain due to the high degree of uncertainty in the magnitude of clinical benefit of tofersen plus background therapy compared to background therapy alone and the uncertainties related to whether the clinical benefits modelled would be realized as the economic model structure does not reflect clinical practice. A price reduction in excess of 90%, in addition to reductions in the cost of background therapy and/or nondrug costs incurred by the health system would be required to achieve cost-effectiveness at a \$50,000 per QALY threshold. Price reductions for different thresholds are available in Appendix 4 in the Pharmacoeconomic Review report.	—

ALS = amyotrophic lateral sclerosis; CDEC = Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Discussion Points

- Reconsideration request:** The sponsor requested a minor reconsideration of the initial draft recommendation to reimburse tofersen with conditions for the treatment of adults with ALS associated with a mutation in the *SOD1* gene. During the minor reconsideration discussion, a committee subpanel discussed the issue raised by the sponsor in their request for reconsideration, which requested to allow the concomitant use of tofersen and edaravone. CDEC also discussed feedback from the drug plans, patient groups, clinician groups, and clinical experts on the initial draft recommendation.
- Criteria for significant unmet need are met:** CDEC noted that there was uncertainty with the clinical evidence; therefore, the committee deliberated on tofersen considering the criteria for significant unmet need described in the *Procedures for Reimbursement Reviews*. *SOD1* ALS affects approximately 40 people in Canada, is uniformly fatal within few years, and has no disease-modifying therapy. Given this rarity, severity, and lack of alternatives, the committee accepted lower-certainty evidence (low or very low Grading of Recommendations Assessment, Development and Evaluation [GRADE] for clinical end points) because the available data suggest tofersen may have a potentially promising, but unconfirmed, effect in slowing functional decline.
- Clinical evidence:** CDEC acknowledged the low to very low certainty of the 28-week results from the VALOR study. However, it considered the longer-term data from the 52- and 104-week

extension periods, supported by evidence of target engagement with neurofilament light chain (NfL) combined with the significant unmet need, as sufficient to infer a potential disease-modifying effect. Despite these considerations, CDEC also noted that the available evidence, particularly from the controlled phase of the VALOR trial, does not conclusively demonstrate a clinical benefit. The Notice of Compliance with Conditions granted by Health Canada for tofersen reflects this evidentiary uncertainty and underscores the regulatory requirement for confirmatory studies to establish definitive clinical efficacy. While biomarker improvements and trends in uncontrolled data suggest a potential therapeutic benefit, robust evidence confirming clinical effectiveness is still needed.

- **Discontinuation safeguards:** CDEC agreed that permanent full-time ventilation or transition to comfort-focused care — at which point the benefit–risk or benefit–burden balance becomes unfavourable — may be appropriate discontinuation criteria that align with the clinical expert input and the VALOR trial's safety findings.
- **Real-world clinical experiences:** The clinical experts reported real-world experiences in which patients with *SOD1* ALS appeared to derive meaningful clinical benefits from tofersen in routine practice settings. These benefits may include stabilization or slowing of disease progression relative to expected clinical trajectories. CDEC also acknowledged input from patient groups that reported both patient- and caregiver-observed tangible improvements in physical function and a perceived slowing of functional decline following treatment with tofersen.
- **Prescribing and service-delivery considerations:** CDEC discussed that monthly intrathecal dosing requires trained proceduralists and cold-chain storage but typically can be delivered in outpatient procedure suites without routine hospital admission. Jurisdictions may need hub-and-spoke or mobile models to serve patients who live in rural areas; therefore, the tofersen conditions allow for lumbar puncture delegation under ALS centre oversight while reserving prescription and renewal authority for ALS specialist neurologists or physiatrists. Though the delivery of tofersen in outpatient settings may alleviate some access barriers, these barriers may persist for persons living in rural and remote settings and be exacerbated by the physical impacts of ALS.
- **Comparator use (riluzole with or without edaravone):** During the initial and reconsideration meetings, CDEC acknowledged the clinical experts' opinions suggesting that continued use of riluzole is likely to become standard clinical practice. The clinical experts also noted that the concomitant use of tofersen with edaravone, or in combination with both riluzole and edaravone, is unlikely to be widely adopted in clinical practice. They also emphasized that tofersen offers the most promising potential to modify disease progression in patients with *SOD1* ALS. Although evidence on the safety and efficacy of triple therapy (i.e., tofersen with riluzole and edaravone) or the combined use of tofersen and edaravone is limited, CDEC noted that the VALOR study included some patients receiving edaravone, the 2 drugs have different mechanisms of action, *SOD1* ALS is a rare condition, and the combination of tofersen and edaravone is used in a very small patient population. Based on these considerations, CDEC concluded that clinicians should have the flexibility to prescribe both tofersen and edaravone. CDEC also emphasized that this decision should not be considered a precedent for future treatment evaluations, as each case is assessed individually.

- Diagnostic testing procedure considerations:** The committee discussed that testing for *SOD1* mutations is currently performed as the standard of care for patients with ALS in Canada and acknowledged that evaluating *SOD1* mutation status before the initiation of tofersen would be required. The CDA-AMC base-case reanalysis (i.e., cost-effectiveness and budget impact analysis) excluded the costs of *SOD1* mutation testing given that the reimbursement of tofersen is not expected to increase overall testing volume. The committee noted that, at present, *SOD1* mutation testing is funded by drug sponsors, and that capacity varies across jurisdictions. The clinical experts and the committee discussed concerns with the lack of clarity on the long-term availability of sponsor-funded testing. Discontinuation of the sponsor-funded panel could shift demand to publicly funded laboratories, increase costs, and/or pose barriers to access. CDEC noted that, in such an instance, the cost of *SOD1* mutation testing would have budgetary implications to the public health care system. It was also emphasized that the cost of *SOD1* mutation testing must be addressed and be appropriately accessible in the context of neuromuscular disease.
- Cerebrospinal fluid (CSF) *SOD1* or plasma NfL:** CDEC noted that serial assays of CSF *SOD1* or plasma NfL are research only, inconsistently available, and not required for routine monitoring; consequently, these biomarkers were not considered as basis for renewal or discontinuation.
- Ethical considerations:** CDEC discussed ethical and equity considerations related to tofersen for *SOD1* ALS, including the significant physical, emotional, and financial burdens of *SOD1* ALS for patients and caregivers. Regarding uncertainties in the clinical evidence, CDEC discussed how this might complicate decision-making by patients, clinicians, and health systems, especially for and about groups that were underrepresented or excluded from the trial populations. CDEC also discussed the risks and burdens associated with the intrathecal delivery of tofersen, in terms of delivery and access, and patient risks and experiences. They noted the enhanced expectations of patients living with ALS and their caregivers for disease-modifying therapies and how these should be accounted for when considering the potential benefits, harms, and evidentiary uncertainties associated with tofersen.
- Economic considerations:** The committee discussed the economic evidence for tofersen and noted that tofersen plus background therapy was associated with 0.76 incremental QALYs and 1.93 incremental life-years at an additional cost of \$1,205,885. The incremental cost is driven by drug acquisition costs, which make up 98% of the total costs associated with treatment with tofersen plus background therapy. CDEC expressed significant concerns regarding the cost-effectiveness of tofersen. The CDA-AMC base-case ICER was considered to be unacceptably high based on the magnitude of the incremental cost and the clinical benefit observed. The committee noted that the results of the analysis are driven by a predicted improvement in life expectancy associated with tofersen, which results in both additional drug acquisition costs for background therapy and nondrug-related costs (i.e., drug administration, monitoring, disease management, and side effects). The committee noted the uncertainty associated with the underlying clinical evidence, particularly the lack of demonstrated benefit in reducing mortality. To achieve cost-effectiveness at a \$50,000 per

QALY threshold, reductions would be required to not only the price of tofersen but also to the cost of background therapy and/or the nondrug costs incurred by the health system.

- **Societal perspective:** CDEC discussed the sponsor's societal perspective analysis, which included indirect costs associated with health states and potential negative impacts on caregiver HRQoL. CDEC noted that indirect costs and outcomes were not assessed in the VALOR trial and that no evidence was submitted by the sponsor to support an impact of tofersen on these costs or outcomes. The incremental costs and QALYs predicted in the sponsor's societal analysis are highly uncertain due to a lack evidence of the societal impact of tofersen, the uncertainty associated with the chosen model inputs, and the omission of productivity loss that was noted to be relevant to patients according to the patient input received. The committee deemed that the results of this analysis were too uncertain to inform decision-making.

Background

ALS is a rare, progressive, and fatal neurodegenerative disease characterized by the loss of motor neurons, which leads to progressive muscle weakness, loss of function, and, typically, death from respiratory failure within 3 to 5 years of diagnosis. *SOD1* ALS, an ultrarare genetic subtype caused by mutations in the *SOD1* gene, affects an estimated 40 individuals in Canada, where the overall ALS prevalence is approximately 6.84 per 100,000 people. Key symptoms of ALS include muscle weakness and difficulties with mobility, speech, swallowing, and breathing, which severely impact daily activities and quality of life.

Current treatments for ALS, such as riluzole and edaravone, provide modest benefits in slowing ALS progression or extending survival for some patients. However, they do not address the underlying genetic cause of *SOD1* ALS or significantly alter the disease course. Patients and clinicians emphasized that a critical unmet need remains for disease-modifying therapies that can slow progression, preserve function, improve survival, and target the specific pathology of genetic forms of ALS like *SOD1* ALS.

Tofersen has been approved by Health Canada for the treatment of adults with ALS associated with a mutation in the *SOD1* gene. Tofersen is an antisense oligonucleotide that is complementary to a portion of the 3 prime untranslated region of messenger ribonucleic acid (mRNA) for human *SOD1* and binds to the mRNA by Watson–Crick base pairing (hybridization). It is available as a 100 mg/15 mL (6.7 mg/mL) solution for intrathecal injection.

Tofersen is administered intrathecally using lumbar puncture by, or under the direction of, health care professionals experienced in performing lumbar punctures. The recommended dose of tofersen is 100 mg/15 mL (6.7 mg/mL) and treatment should be initiated with 3 loading doses administered at 14-day intervals (day 0, day 14, and day 28) with a maintenance dose every 28 days thereafter (day 56, day 84, and so forth).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal phase III, randomized, double-blind, placebo-controlled study in adults with ALS and a confirmed *SOD1* mutation; 1 open-label, long-term extension (OLE) study; and 4 real-world studies included in the Studies Addressing Gaps, Description of Studies — German and Italian Early Access Program section
- patients' perspectives gathered by 4 patient groups, the ALS Society of Canada, ALS Action Canada, the ALS Society of Alberta, and the ALS Society of British Columbia
- input from public drug plans that participate in the reimbursement review process
- 5 clinical specialists with expertise diagnosing and treating patients with ALS
- input from 1 clinician group, the Canadian ALS Research Network (CALS)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to tofersen
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Patient input was submitted by the ALS Society of Canada, ALS Action Canada, the ALS Society of Alberta, and the ALS Society of British Columbia. Information was gathered from patients and caregivers through an online survey, interviews, and focus groups. Among the groups, more than 20 respondents living with ALS had experience with tofersen.

The input noted that ALS severely impacts patients' mobility, strength, daily activities, and emotional health. Key symptoms include muscle weakness, balance issues, cramping, nerve pain, and difficulty speaking, swallowing, and breathing. Limited mobility hinders independence, which affects tasks like climbing stairs, carrying groceries, or prolonged standing. Emotional tolls include fear of disease progression, anxiety about future independence, and the burden on loved ones. For those with familial ALS, the disease is deeply personal, as many have seen its effects on loved ones, leading to significant emotional and psychological strain. Within a year of diagnosis, patients reported needing help from caregivers with daily tasks like eating, walking, and bathing. The input noted that patients with ALS, facing a progressive and fatal illness, often pursue all viable treatments, including clinical trials, alternative therapies, and off-label options. The input stated that in Canada, ALS treatments include riluzole and edaravone, which may provide some benefit but do not significantly alter disease progression. Furthermore, some patients indicated difficulty accessing edaravone due to a lack of private coverage, strict public funding criteria, out-of-pocket costs, and supply shortages. The input noted that neither therapy specifically addresses the *SOD1* gene mutation in ALS.

Patients who have had experience with tofersen reported benefits such as maintaining independence and delaying symptom onset, allowing them to maintain activities that were previously becoming difficult, and the ability to spend more time with loved ones. Patients noted that lumbar punctures to administer tofersen pose logistical challenges as the patients often needed to travel long distances to receive treatment, as well as physical challenges with adverse effects such as headaches, migraines, nausea, and temporary incapacitation. The input stated that improved protocols, such as slow injections and localizing administration to nearby clinics, could enhance accessibility and patient experience. The input emphasized the importance of early and accessible genetic testing for timely intervention with tofersen. Respondents found their experiences with genetic testing to be efficient with timely results and minimal cost barriers. The most critical unmet needs according to the patient group input include symptom reversal (i.e., muscle weakness, cramping, and fasciculations); maintenance of mobility, function, and independence; slowing disease progression; increased survival; and improved quality of life.

Clinician Input

Input From Clinical Experts Consulted for This Review

The information in this section is based on input received from a panel of 5 clinical specialists consulted by CDA-AMC for the purpose of this review.

According to the clinical experts consulted by CDA-AMC for this review, the primary unmet need for patients with *SOD1* ALS before the availability of tofersen was the lack of treatments capable of significantly altering the disease course. Existing therapies like riluzole and edaravone were considered to offer only modest effects, failed to halt or reverse functional decline, and did not target the underlying genetic cause. The experts viewed a treatment targeting the mutant *SOD1* protein as a critical gap. They also identified challenges such as geographical disparities in access to specialized ALS care, inconsistent access to timely and funded *SOD1* genetic testing, and the resource implications of administering monthly intrathecal injections.

The clinical experts consulted view tofersen as a first-line, disease-modifying therapy for adults with symptomatic ALS confirmed to be caused by a pathogenic *SOD1* mutation, as it directly targets the underlying disease mechanism. They advised that treatment should be initiated as soon as an ALS specialist confirms the diagnosis, emphasizing that early initiation is critical to preserve motor neurons and maximize potential benefits. The experts suggested that riluzole and, where feasible, edaravone would typically be continued alongside tofersen for potential additive benefits, but patients should not be required to try these other drugs or have ALS disease that has not responded to them before accessing tofersen.

The patient population identified by the experts as most likely to benefit from tofersen includes adults with a confirmed pathogenic *SOD1* mutation who are symptomatic with ALS but still retain sufficient residual motor function. They noted that individuals with rapidly progressive phenotypes and younger individuals would have the greatest need. Conversely, the experts considered patients with very advanced disease (e.g., anticipated survival < 6 months, inability to tolerate a lumbar puncture) and those considered presymptomatic carriers (outside of research settings) as least suitable for therapy.

In terms of assessing response to treatment, the experts indicated this is primarily done through clinical evaluation by an ALS specialist, typically every 3 months, focusing on monitoring the rate of functional decline for stabilization or slowing of progression. Key clinical tools mentioned were manual muscle testing, patient-reported function, and respiratory assessment using forced vital capacity. While many end points used in the VALOR trial (SVC, handheld dynamometry [HHD], specific quality of life scales, and biomarkers like CSF SOD1 protein and plasma NfL) are not standard tools for routine clinical decision-making in Canada, the experts noted that ALSFRS-R score is used during follow-up visits to measure the score and monitor the change in the slope of the ALSFRS-R score, which the clinical experts identified as clinically meaningful. A clinically meaningful response, according to the experts, involves the stabilization or slowing of disease progression; any improvement in function is highly significant but not always the primary expectation. The patient's and clinician's perception of benefit relative to the burden of treatment is considered crucial.

Regarding discontinuing treatment, the clinical experts agreed that defining absolute objective criteria is difficult. Key reasons for discontinuation identified by the experts include patient preference due to a perceived lack of benefit or the burden of monthly treatment, intolerable or unmanageable adverse events (AEs) (such as severe neurologic inflammation or papilledema), the physical inability to perform the lumbar puncture, or reaching a very advanced, end-stage disease state where the potential for benefit is considered negligible. The need for permanent ventilation often prompts discussions about discontinuation. However, the experts noted that continued disease progression alone is usually not a trigger for stopping treatment unless the disease becomes extremely advanced or the patient chooses to discontinue treatment.

Additional considerations highlighted by the experts included the need for diagnosis and treatment initiation to be led by neurologists or physiatrists with ALS expertise, though administration could be delegated to clinicians proficient in lumbar puncture. They noted that most injections occur in outpatient settings but acknowledged logistical challenges, particularly for patients from rural and remote areas, and the need for sustainable resources. Periodic ophthalmologic examinations were advised due to the risk of elevated intracranial pressure. The experts also underscored the need for expanded publicly funded genetic testing and research into less burdensome delivery systems and biomarker-guided dosing.

Clinician Group Input

One clinician group, CALS, which consisted of 14 clinicians, provided input for this review. The submission noted that ALS is a progressive neurodegenerative disease that leads to the degeneration of motor neurons in the brain and spinal cord, which results in severe weakness in limb, bulbar, and respiratory muscles, and eventually causes loss of autonomy and dependence on assistive devices like wheelchairs, feeding tubes, and ventilatory support. Most patients die from respiratory failure within 5 years of diagnosis. The experts noted that available ALS treatments include riluzole, which extends survival by about 3 months by targeting glutamate, and IV or oral edaravone, which may slow disease progression in some patients. Albrioxa was approved in 2022, however, it was withdrawn in 2024 after failing a phase III clinical trial. The input noted that these treatments provide only modest benefits and do not reverse the disease or halt its progression and there are currently no approved treatments specifically targeting hereditary ALS. The clinicians emphasized

the urgent need for personalized, disease-modifying treatments. Ideal therapies would slow progression, improve quality of life, target the root causes of ALS, and reduce the burden on caregivers. Given the complexity of ALS, treatments should be tailored to individual patients, prevent motor neuron degeneration, and incorporate precision medicine approaches.

The input stated that tofersen is best suited for patients with ALS who have pathogenic, or likely pathogenic, *SOD1* gene mutations and weakness linked to ALS, as determined by a specialist. Patients with uncertain *SOD1* variants tied to the disease may also be eligible. As there is no diagnostic biomarker for weakness related to ALS, a diagnosis is made based on a patient's history, physical examination, electrodiagnostic examination, and exclusion of alternative diagnoses. Upon diagnosis, all patients with ALS should undergo genetic testing for common ALS-related genes, including *SOD1*. If an *SOD1* mutation is identified, patients should be promptly considered for the drug under review. The input stated that tofersen would be used in combination with existing therapies, creating a multimodal approach that addresses multiple disease pathways. The input noted that there is no rationale for requiring patients to have disease that failed on other therapies before initiating tofersen, given the irreversible progression of ALS. The clinicians also noted that treatment response or failure for ALS is not precisely defined as the primary goal of treatment is to slow the degeneration of motor neurons. Individual disease progression varies and tracking outcomes like slowed progression is challenging due to disease heterogeneity. An appropriate treatment strategy involves initiating the drug and monitoring the patient at regular intervals until care goals transition to a more palliative approach or the patient and physician decide to stop treatment based on an unfavourable risk-benefit assessment.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for tofersen:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- care provision issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Is there any evidence to support the addition of riluzole and/or edaravone once a patient's disease is stable on tofersen?	There is no direct evidence to confirm benefit or harm from triple therapy; however, the experts see no biological reason to withhold riluzole or edaravone and believe a modest additive benefit is plausible. In practice, most centres will continue riluzole — and, where funded and tolerated, edaravone — alongside tofersen, while acknowledging that some patients or provinces may choose tofersen monotherapy to reduce pill burden or cost. CDEC acknowledged the clinical experts opinion that continued use of riluzole is likely to become standard clinical practice. While the evidence supporting the efficacy and safety of triple therapy (i.e., tofersen in combination with riluzole and edaravone), or concomitant use of tofersen and edaravone, is limited, CDEC noted that clinicians should have the flexibility to prescribe both tofersen and edaravone.
Considerations for initiation of therapy	
Ongoing measurement of <i>SOD1</i> mutations and NfL are required to measure intermediate outcomes. Are these standard tests that can be undertaken in all provinces where patients are treated?	The clinical experts noted to CDEC that for <i>SOD1</i> mutations, genetic testing is performed at diagnosis to confirm eligibility for treatments like tofersen. However, once a pathogenic <i>SOD1</i> mutation is identified, ongoing or repeat measurement of the mutation itself is not considered necessary or standard practice, as the genetic mutation does not change. The initial diagnostic testing for <i>SOD1</i> mutations does face variability in access across Canada, with some provinces having in-house capabilities and others relying on out-of-province or out-of-country testing, sometimes facilitated by sponsored panels whose long-term availability is uncertain. Serial measurement of the CSF <i>SOD1</i> protein is not feasible in routine practice: the assay is research only, unavailable in clinical laboratories in Canada, and clinicians do not consider it necessary for treatment monitoring. The availability of NfL measurement as a standard test for ongoing monitoring is also inconsistent across Canadian provinces. While NfL assays are commercially available and used in some specialized clinics (e.g., in Alberta) to assess target engagement and as a prognostic marker, they are not routinely publicly funded or widely accessible in many other jurisdictions, like Ontario or Saskatchewan. Experts have indicated that while NfL is a valuable research tool and can show target engagement, its individual-level predictive value for clinical outcomes or its utility in making ongoing treatment decisions (such as continuation or discontinuation of therapy) is an area of ongoing research where targeting normal levels is an intuitive goal. CDEC noted that CSF <i>SOD1</i> concentrations and plasma NfL levels are not considered reliable indicators for assessing clinical response to tofersen therapy. While these biomarkers may demonstrate target engagement or biological activity, they do not provide sufficient evidence of therapeutic efficacy or correlate consistently with meaningful clinical outcomes.

Implementation issues	Response
Can the drug be given again to patients whose disease relapsed while they were off therapy due to side effects or who discontinued the treatment for other reasons?	CDEC agreed with the experts that the reason for the initial stoppage is important; for instance, if it was due to temporary factors (like moving or pregnancy), or patient preference at the time, restarting could be considered. However, if the discontinuation was due to significant side effects, such as severe inflammatory reactions like myelitis or papilledema, the risks associated with re-exposure would need careful evaluation, and the potential outcome of restarting in such specific cases is considered unknown. The decision would likely involve a risk-benefit analysis in the context of the patient's condition and the nature of the previous adverse event.
Considerations for continuation or renewal of therapy	
Despite evidence that tofersen had biological effects, the primary analysis at week 28 of the VALOR trial did not show a statistically significant difference between tofersen and placebo. What would be the length of time approved for treatment given these results? Is treatment to continue long term without any discontinuation parameters besides permanent ventilation?	The experts noted that a 6-month trial is too short for a gene-targeted therapy whose clinical effects emerge after biomarker normalization. The experts pointed to promising trends from the open-label extension trial and real-world use that support sustained benefit over years. Regarding the approved length of treatment, the consensus among the consulted experts leans toward recommending long-term treatment approval without a predefined stop date, contingent on ongoing benefit perceived by the patient and clinician. Treatment continuation should generally occur as long as the benefits are deemed to outweigh the risks and burdens, particularly the monthly intrathecal injections. The clinical experts considered permanent invasive ventilation as a reasonable default stop point, although ultimate decisions should reflect patient preference and clinician judgment of ongoing benefit. Besides permanent ventilation (via tracheostomy or, potentially, 24/7 noninvasive ventilation), which is a common discontinuation point for other ALS therapies and was supported by some experts as a potential end point for tofersen, other parameters discussed include: • patient preference or transition to palliative care • intolerable or unmanageable serious adverse events, such as severe myelitis or papilledema affecting vision • practical inability to administer the drug; for instance, if a patient can no longer be positioned for a lumbar puncture • reaching a very advanced stage where, in the clinician's and patient's view, there are no longer functional motor neurons to preserve, though defining this stage precisely was acknowledged as difficult. CDEC recommended that tofersen therapy be discontinued in patients who transition to permanent ventilatory support or comfort-focused care.
Considerations for discontinuation of therapy	
What would be the criteria for discontinuation of therapy?	The committee discussed the following points as consideration for discontinuation: • serious inflammatory or pressure-related adverse events (e.g., aseptic meningitis, inflammatory myelitis, refractory intracranial hypertension with threatened vision) do not respond to standard management • technical inability to perform safe lumbar puncture • the patient reaches an advanced palliative stage with no functional motor neurons left to preserve • the patient elects to stop treatment.

Implementation issues	Response
	CDEC recommended that tofersen therapy be discontinued in patients who transition to permanent ventilatory support or comfort-focused care.
Considerations for prescribing of therapy	
Intrathecal administration requires special training and facilities. Is this available in all jurisdictions? Can any neurologist be trained to administer this medication? Does intrathecal administration require inpatient admission to a hospital or administration in an outpatient clinic? If yes, this has implications for which budget and/or program would pay for tofersen.	Tofersen must be prescribed by an ALS expert neurologist or physiatrist, but any clinician competent in lumbar puncture (e.g., neurologist, anesthesiologist, interventional radiologist, many emergency physicians, some nurse practitioners) can give the dose after a brief orientation. Procedures are normally done in outpatient procedure rooms, day-surgery units, or community hospitals; routine inpatient admission is unnecessary, which keeps the cost in the outpatient or hospital clinic budget rather than acute care beds. Minimal equipment (an exam room, sterile LP kit, and pharmacy cold-chain storage) is needed. Geographic disparities in procedural capacity and anesthesia support remain a bottleneck, so hub-and-spoke or mobile models may be needed for rural areas. CDEC agreed with the clinical experts.
Care provision issues	
Who would be purchasing the drug? The hospital? Community pharmacy or specialty pharmacy? Specialty pharmacies would need a contract in place and this could affect the cost of acquiring tofersen.	Distribution pathways are still being negotiated. Panellists expect most jurisdictions to route purchasing through hospital-based special services pharmacies or contracted specialty pharmacies that can manage cold-chain storage and controlled-access biologics; community retail pharmacies are viewed as unlikely partners. The final arrangements will influence acquisition costs and may require provincial contracts with the manufacturer.

ALS = amyotrophic lateral sclerosis; CDEC = Canadian Drug Expert Committee; CSF = cerebrospinal fluid; LP = lumbar puncture; NFL = neurofilament light chain.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included part C of 1 pivotal phase III, randomized, double-blind, placebo-controlled study (VALOR) and its multicenter OLE study (Study 102). Part C of the VALOR study (N = 108 randomized participants) assessed the efficacy, safety, and tolerability of tofersen 100 mg administered intrathecally compared to placebo over 28 weeks in adults with ALS and a confirmed *SOD1* mutation. Randomization was 2:1 (tofersen N = 72; placebo N = 36). The primary end point was change from baseline to week 28 in ALSFRS-R total score in the modified intent-to-treat (mITT) population (N = 60), defined as participants who met the prognostic enrichment criteria for faster disease progression. ALSFRS-R is a 12-item scale that assesses function in 4 domains, including respiratory, bulbar, gross motor, and fine motor. Each item is rated on a scale of 0 to 4, generating an ALSFRS-R total of score of 0 (maximum disability) to 48 (no disability). Secondary outcomes included changes in total SOD1 protein in CSF, NFL in plasma, SVC, HHD megascore,

and time to death or permanent ventilation. Participants who completed the VALOR study could enrol in the OLE study to receive tofersen.

In the VALOR trial, the overall intention-to-treat (ITT) population (N = 108) had a mean age of 49.2 years (standard deviation [SD] = 12.3); 57.4% were males and 42.6% were females. Race was reported as

[REDACTED]. The mean ALSFRS-R total score at baseline was 37.1 (SD = 5.9). In the mITT faster progression subgroup (N = 60), the mean age was 49.7 years (SD = 14.3) and the mean baseline ALSFRS-R score was 35.8 (SD = 6.1). Baseline plasma NfL levels in the ITT population were a mean of 96.9 pg/mL (SD = 84.2). The majority of participants in the ITT population had limb-onset ALS (placebo group = 72% lower and 19% upper; tofersen group = 64% lower and 28% upper).

In this section, only part C of the VALOR study is presented; the first 2 parts of VALOR study (parts A and B) were dose-escalation trials conducted to assess the dose of tofersen to be used in part C. Patients who were enrolled in parts A and B of the VALOR study were not enrolled in part C of the study.

Efficacy Results

In the VALOR study's randomized phase, the primary analysis, the change from baseline to week 28 in ALSFRS-R total score in the mITT faster progression population (N = 60) showed an adjusted mean difference between tofersen (−6.98 points from baseline) and placebo (−8.14 points from baseline) of 1.2 points (95% confidence interval [CI], −3.2 to 5.5; P = 0.9689; joint rank test with multiple imputation). A post hoc analysis in the ITT population (N = 108) that adjusted for baseline NfL showed an adjusted mean difference in ALSFRS-R score of 1.4 points (95% CI, −1.34 to 4.09; nominal P = 0.3218) favouring tofersen (−4.5 points from baseline) over placebo (−5.8 points from baseline).

Key secondary end points in the VALOR trial at week 28 included:

- Total CSF *SOD1* protein (mITT): Tofersen resulted in a geometric mean ratio (GMR) to baseline of 0.71, while placebo was 1.16. The difference in GMR for tofersen to placebo was 0.62 (95% CI, 0.49 to 0.78; nominal P < 0.0001).
- Plasma NfL (mITT): Tofersen resulted in a GMR to baseline of 0.40, while the GMR for placebo was 1.20. The difference in GMR for tofersen to placebo was 0.33 (95% CI, 0.25 to 0.45; nominal P < 0.0001).
- Percent predicted SVC (mITT): The adjusted mean change from baseline was −14.31 percentage points for tofersen and −22.20 percentage points for placebo, an adjusted mean difference of 7.9 percentage points (95% CI, −3.5 to 19.3; nominal P = 0.1755, ANCOVA plus multiple imputation).
- HHD megascore (mITT): The adjusted mean change from baseline was −0.34 for tofersen and −0.37 for placebo, an adjusted mean difference of 0.02 points (95% CI, −0.21 to 0.26; nominal P = 0.8390).
- Time to death or permanent ventilation (mITT): Few events occurred — 4 in the tofersen group and 2 in the placebo group; the hazard ratio was 1.39 (95% CI, 0.219 to 8.803).

In the OLE study (data cut-off date of February 28, 2023; ITT population from the VALOR trial), comparing early-start tofersen (randomized to tofersen in the VALOR trial) to delayed-start tofersen (randomized to placebo in the VALOR trial, then initiated tofersen in the OLE study):

- ALSFRS-R score: At week 52, the adjusted mean difference was 3.5 points (95% CI, 0.4 to 6.7; nominal P = 0.0272) favouring early-start tofersen. At week 104, the difference was 3.7 points (95% CI, -0.7 to 8.2; nominal P = 0.1004).
- Biomarkers: Reductions in CSF SOD1 protein and plasma NfL were sustained in the early-start group and observed in the delayed-start group after initiating tofersen. At week 104, plasma NfL GMR from baseline was [REDACTED] for early-start tofersen and [REDACTED] for delayed-start tofersen.
- Percent predicted SVC: At week 104, the adjusted mean difference was [REDACTED] percentage points favouring early-start tofersen.
- Time to death or permanent ventilation: The hazard ratio for early-start tofersen versus delayed-start tofersen was [REDACTED] (95% CI, [REDACTED]).

Harms Results

In the VALOR study (safety population N = 108), AEs were reported by 95.8% (69 of 72) of participants in the tofersen group and 94.4% (34 of 36) of participants in the placebo group. The most common AEs ($\geq 20\%$ in either group) were procedural pain (tofersen: 56.9%; placebo: 58.3%), headache (tofersen: 45.8%; placebo: 44.4%), pain in extremity (tofersen: 26.4%; placebo: 16.7%), fall (tofersen: 23.6%; placebo: 41.7%), back pain (tofersen: 20.8%; placebo: 5.6%), and post-lumbar puncture syndrome (tofersen: 18.1%; placebo: 30.6%).

Serious adverse events (SAEs) occurred in 18.1% (13 of 72) of participants in the tofersen group and 13.9% (5 of 36) of participants in the placebo group during the VALOR trial. The most frequently reported SAEs included dyspnea, pulmonary embolism, and aspiration pneumonia. Withdrawals due to AEs occurred in 5.6% (4 of 72) of the tofersen group and 0% of the placebo group. One death (congestive cardiac failure, which was not considered treatment related) occurred in the tofersen group during the VALOR study.

Notable harms included serious neurologic events reported in 5.6% (4 of 72) of participants treated with tofersen (e.g., lumbar radiculopathy, chemical meningitis, myelitis, transverse myelitis) and none in the placebo group. Falls were less frequent in the tofersen group (23.6%) compared to the placebo group (41.7%). CSF abnormalities (e.g., increased white blood cell count, increased protein) were more common in the tofersen group (16.7%) than the placebo group (2.8%).

In the OLE study (N = 104; data cut-off date of February 28, 2023), [REDACTED] experienced AEs. SAEs were reported by [REDACTED] of participants. AEs leading to drug discontinuation occurred in [REDACTED] of participants. A total of [REDACTED] occurred during the VALOR and OLE studies. The safety profile in the OLE study was generally consistent with the VALOR study, with common AEs reflecting ALS progression or lumbar puncture procedures. Serious neurologic events like myelitis, radiculitis, aseptic meningitis, and papilledema continued to be observed.

Critical Appraisal

The internal validity of the VALOR trial is impacted by several factors. Critically, the trial did not meet its prespecified primary efficacy end point for ALSFRS-R score at 28 weeks. Subsequent analyses, including those in the ITT population and those showing effects on biomarkers, relied on post hoc adjustments (e.g., for baseline NfL levels) or were exploratory due to the primary end point failure, increasing the risk of type I error. While methods of randomization and blinding were appropriately applied in the pivotal phase, baseline imbalances were noted, and the study was underpowered and likely had a too-short duration for its clinical end points, leading to imprecision in its effect estimates. The reliance on surrogate biomarkers (CSF *SOD1* and plasma NfL), though showing nominal statistically significant changes, means their direct clinical meaningfulness remains unvalidated. The OLE study has inherent limitations, including the lack of randomization and a concurrent control group, high participant attrition over time, and the potential for detection bias, which tempers confidence in the long-term findings.

Regarding external validity, the VALOR trial population was enriched for participants with faster disease progression and specific *SOD1* mutations, which may limit the generalizability of the main findings to the broader, more heterogeneous population with *SOD1* ALS, including those with slower progression. While patients with a slower progression of ALS were enrolled, they were not part of the main analysis and, due to the disease nature and trial timeline, were not expected to experience a difference. Participants were predominantly white, which is consistent with the known epidemiology of ALS. Furthermore, many of the outcome measures employed were primarily research tools, which are not routinely used for clinical decision-making in Canada, and the short 6-month blinded phase was insufficient to definitively assess effects on survival or functional measures. Finally, the evidence lacks comparison against standard therapeutic options in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- change from baseline to week 28 on ALSFRS-R total score
- GMR of baseline to week 28 on total CSF *SOD1* protein
- GMR of baseline to week 28 on plasma NfL
- change from baseline to week 28 on SVC percent predicted
- change from baseline to week 28 on HHD megascore
- time to death or permanent ventilation
- SAEs.

Table 3: Summary of Findings for Tofersen vs. Placebo for Patients With *SOD1* ALS

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Tofersen	Difference		
Change from baseline to week 28 on ALSFRS-R total score							
Change from baseline on ALSFRS-R total score (mITT — faster progression group) (more is better) Follow-up: week 28	60 (1 RCT)	NA	−8.14 points	−6.98 points	1.2 more points (3.2 fewer points to 5.5 more points)	Low ^{a,b}	Tofersen may result in little or no clinically meaningful difference in ALSFRS-R score compared to placebo.
Change from baseline on ALSFRS-R total score (ITT — total patients post hoc analysis adjusted for baseline NfL levels) (more is better) Follow-up: week 28	108 (1 RCT)	NA				Very low ^{a,c}	The evidence is very uncertain about the effect of tofersen on ALSFRS-R score when compared to placebo.
GMR to baseline to week 28 on total CSF SOD1 protein							
Total CSF SOD1 protein geometric mean ratio to baseline (mITT — faster progression group) (less is better) Follow-up: week 28	60 (1 RCT)	0.62 (0.49 to 0.78)	1.16	0.71 (0.62 to 0.83)	NA	Moderate ^{d,e}	Tofersen likely results in a decrease in CSF SOD1 protein geomatric mean ratio compared to placebo.
GMR to baseline to week 28 on plasma NfL							
Plasma NfL geometric mean ratio to baseline (mITT — faster progression group) (less is better) Follow-up: week 28	60 (1 RCT)	0.33 (0.25 to 0.45)	1.20	0.40 (0.33 to 0.48)	NA	Moderate ^{d,e}	Tofersen likely results in a decrease in NfL geometric mean ratio compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Tofersen	Difference		
Change from baseline to week 28 on SVC percent predicted							
Change from baseline in percent predicted SVC (mITT — faster progression group) (more is better) Follow-up: week 28	60 (1 RCT)	NA	−22.20 percentage of predicted	−14.31 percentage of predicted (−██████████)	7.9 more percentage of predicted (3.5 less points to 19.3 more points)	Low ^{b,f}	Tofersen may result in little or no clinically meaningful difference in SVC score compared to placebo.
Change from baseline to week 28 on HHD megascore							
Change from baseline in HHD megascore (mITT — faster progression group) (more is better) Follow-up: week 28	60 (1 RCT)	NA	−0.37	−0.34 (−██████████)	0.02 more points (0.21 less points to 0.26 more points)	Low ^{b,f}	Tofersen may result in little or no clinically meaningful difference in HHD score compared to placebo.
Time to death or permanent ventilation							
Patients with an event of death or permanent ventilation (mITT — faster progression group) (more is better) Follow-up: week 28	60 (1 RCT)	Hazard ration = 1.39 (0.219 to 8.803)	2 patients	4 patients	NA	Very low ^g	The evidence is very uncertain about the effect of tofersen on the proportion of patients experiencing death or permanent ventilation when compared to placebo.
Median time to death or permanent ventilation ^h	60 (1 RCT)	NA	NA	NA	NA	NA	NA
Harms							
Patients with 1 or more serious adverse events (safety set) (less is better) Follow-up: week 28	108 (1 RCT)	NA	5	13	NA	Very low ⁱ	The evidence is very uncertain about the effect of tofersen on the proportion of patients experiencing serious

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Tofersen	Difference		
							adverse events when compared to placebo.

ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CI = confidence interval; CSF = cerebrospinal fluid; GMR = geometric mean ratio; HHD = handheld dynamometry; ITT = intention to treat; MID = minimal important difference; mITT = modified intention to treat; NA = not available; NfL = neurofilament light chain; RCT = randomized controlled trial; SVC = slow vital capacity; vs. = versus.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. When a published MID was available and judged applicable, that value was used as the threshold for imprecision. When no empirically validated MID was identified (or existing estimates were highly inconsistent), we used thresholds suggested by the clinical experts consulted for this review. If the clinical experts were unable to suggest an MID, we defaulted to the null effect (no difference) as the threshold. The lack of an MID and use of the null effect could result in a 1-level downgrade.

^aRated down 1 level for serious imprecision. The MID for ALSFRS-R score in patients with ALS is very uncertain, based on the varying and wide ranges of MIDs reported in the literature and per clinical expert input. The null effect (no difference) was therefore considered as a threshold for assessment. The 95% CI for the difference is wide and includes the possibility of a potentially clinically meaningful benefit, no meaningful difference, and potential harm. the total sample (N = 60 mITT; 108 ITT) is below the optimal information size (< 400 for continuous outcomes). No further downgrade was applied because larger studies may not be feasible in this ultrarare condition.

^bRated down 1 level for study limitations. The primary clinical end point (ALSFRS-R score in mITT) was not met; thus, the null hypothesis vs. placebo could not be rejected, imposing an elevated risk of type I error. Similarly, all subsequent results carry high risk of level I error. Furthermore, the study was underpowered and was inappropriately short for this clinical end point. In addition, baseline imbalances were noted in a number of possible treatment effect modifiers. This may result in a bias of an undetermined direction and increased uncertainty in the outcome.

^cRated down 2 levels for serious study limitations. The ALSFRS-R score analysis in the ITT population was a post hoc analysis that included adjustment for baseline NfL, which was an amendment to the statistical analysis plan partway through the trial. This introduces a risk of analysis bias (due to data-driven analysis) and reduces confidence in this specific outcome. Furthermore, the study was underpowered and was inappropriately short for this clinical end point. In addition, baseline imbalances were noted in a number of possible treatment effect modifiers beyond NfL levels. This may result in a bias of an undetermined direction.

^dDid not rate down for imprecision. No MID was found; therefore, the null effect was used and the 95% CI included only the possibility of benefit. Despite the option to downgrade 1 point due to the lack of an important difference threshold, Canada's Drug Agency opted not to due to several factors: mechanistic plausibility, large effect size, and the ultrarare nature of the condition.

^eRated down 1 level for indirectness related to surrogate outcome. The effect estimates for CSF SOD1 protein and plasma NfL reflect biochemical targets rather than patient-important or clinical outcomes. Neither marker has been formally validated as a surrogate that reliably predicts changes in survival, function (ALSFRS-R score), or quality of life in *SOD1* ALS. Consequently, the link from these biomarker shifts to outcomes that matter to patients remains uncertain, warranting a single-level downgrade for indirectness.

^fRated down 1 level for serious imprecision. No MID was found; therefore, the null effect (no difference) was therefore considered as a threshold for assessment. The 95% CI for the difference is wide and includes the possibility of potentially clinically meaningful benefit, no meaningful difference, and potential harm. The total sample (N = 60) is below the optimal information size. No further downgrade was applied because larger studies may not be feasible in this ultrarare condition.

^gRated down 2 levels for very serious imprecision. No minimally important difference was found; therefore, the null effect was used. The 95% CI included very wide possibilities of benefit and harm. The resulting hazard ratio is 1.39 with an extremely wide 95% CI (0.22 to 8.80), spanning an 80% relative reduction to a 780% increase — i.e., clinically important benefit, no effect, and substantial harm are all plausible. For the composite “death or permanent ventilation” end point, the body of evidence comprises 6 total events in 108 participants (4 of 72 vs. 2 of 36). This is far below the optimal information size to assume adequate precision.

^hMedian time to death could not be calculated as there were insufficient events during the trial.

ⁱRated down 2 levels for very serious imprecision. For the serious adverse event outcome, there were only 18 events in 108 participants (13 of 72 vs. 5 of 36). That event count is orders of magnitude below the GRADE optimal information size benchmark of approximately 300 to 500 events for a binary end point — the amount ordinarily needed to rule out a minimal important effect with adequate power. Any relative or absolute treatment effect would exhibit very wide CIs that would include the possibility of harm.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted.

Indirect Comparisons

No indirect comparisons were submitted.

Studies Addressing Gaps, Description of Studies — German and Italian Early Access Program

Four real-world studies evaluated the effectiveness, safety, and patient-reported outcomes of tofersen treatment in patients with *SOD1* ALS enrolled in an early access program (EAP). These included 3 studies from Germany, Wiesenfarth et al., Meyer et al., (2024), and Meyer et al. (2023), and 1 from Italy, Sabatelli et al. The studies included assessments of clinical progression, biomarkers, and HRQoL.

In all 4 studies, tofersen 100 mg was administered directly into the CSF on days 1, 14, and 28 as loading doses. Patients then received up to 16 maintenance doses at intervals of approximately 28 days (with a minimum of 21 days). Across all EAP studies, the ALSFRS progression rate (ALSFRS-PR) was defined as ALSFRS-R score points lost per month. In Meyer et al. (2024), patient-reported outcomes included the Measure Yourself Medical Outcome Profile 2 (MYMOP2), the Treatment Satisfaction Questionnaire for Medication (TSQM-9), and the Net Promoter Score (NPS). The MYMOP2 allows patients to identify and rate the severity of their most troubling symptoms on a 7-point Likert scale (0 for “as good as it could be” to 6 for “as bad as it could be”). The TSQM-9 evaluates treatment satisfaction on effectiveness, convenience, and overall satisfaction (scored from 0 to 100). The NPS assesses the likelihood of recommending the treatment (range, –100 to 100), where scores above 0 indicate more promoters than detractors.

Wiesenfarth et al. followed 24 adults with *SOD1* ALS over 12 months across 10 German centres. The median pretreatment ALSFRS-R score was 37.0 (interquartile range, 29.8 to 41.8). Meyer et al. (2024) included 16 patients with *SOD1* ALS who were assessed for up to 18 months. The mean pretreatment ALSFRS-R score was 37.4 (range, 7 to 46). Meyer et al. (2023) assessed the efficacy of tofersen among 6 patients with unique *SOD1* mutations over a period of at least 5 months. One patient had an ALSFRS-R score of 1 and the remaining patients were considered to have high functional status, with ALSFRS-R scores ranging from 35 to 46 at baseline. Sabatelli et al. reported on 27 of 42 enrolled patients (63.0%) living with *SOD1* ALS; 17 (40.5%) of whom were included in efficacy analysis after exclusions and dropouts.

Efficacy

ALSFRS-PR Score

In Wiesenfarth et al., median ALSFRS-R score declined from 38.0 to 35.0, corresponding to a median ALSFRS-PR score of 0.11 points per month. Seventeen of 23 patients (73.9%) had slowed progression during treatment, while 6 patients (26.1%) had worsened disease. In Meyer et al. (2024), ALSFRS-PR score decreased in 50% of patients with a mean change of –0.2 points per month. In Meyer et al. (2023), ALSFRS-PR score decreased in 2 of 6 patients (33.3%) and no changes were observed in the remaining 4 patients

(66.7%). Sabatelli et al. observed a median ALSFRS-PR score reduction from 0.25 points per month before treatment to 0.0 points per month after treatment.

Biomarkers

Wiesenfarth et al. reported decreased mean serum NfL from 78.0 pg/mL to 36.0 pg/mL and CSF phosphorylated axonal neurofilament heavy chain from 2,226 pg/mL to 1,151 pg/mL. Meyer et al. (2024) observed a 58% decrease in mean serum NfL in 15 of 16 patients (93.8%). Meyer et al. (2023) reported 66% and 62% mean reductions in CSF and serum NfL, respectively. In 14 of 17 patients (82%) in the Sabatelli et al. study, the mean reduction in CSF NfL levels from baseline was 61% (range, 49% to 79%). The remaining 3 patients (17.6%) had unchanged or increased CSF NfL levels.

Health-Related Quality of Life

In Meyer et al. (2024), at baseline, the mean symptom severity on the MYMOP2 7-point scale was 3.8 (n = 14), which decreased to a mean of 3.0 at the last measured perception. From baseline to last measured perception, MYMOP2 responses showed symptom improvement (defined as an improvement in at least 1 of the 2 target symptoms) in 10 of 14 patients (71.4%) and partial improvement (defined as an improvement or stabilization in 1 symptom and deterioration in the other) in the remaining 6 patients (42.9%). TSQM-9 scores were assessed in 15 patients (93.8%) with a mean global satisfaction score of 83 (SD = 16). As assessed by the NPS, at 6 months of tofersen treatment, 12 of 15 patients (80%) were classified as promoters of tofersen.

Harms

In Wiesenfarth et al., common procedure-related side effects included back pain, headache, leg nerve pain, and dizziness. Two patients (8.7%) experienced an SAE possibly related to tofersen during the study, both of whom stopped treatment voluntarily. There were no reported deaths during the observation period. CSF changes indicated autoimmune inflammation in the central nervous system. Eleven of 15 patients (73%) experienced an increase in white blood cells in the CSF and 10 of these patients (66.7%) also experienced elevated protein levels. Nine of 10 patients (90%) showed immune protein production in the CSF.

In Sabatelli et al., postinjection headaches occurred once in 4 patients (23.5%). Seven patients (41.2%) reported limb pain, with pain following the path of a nerve from the spine to the arms or legs. Nine of 15 patients (60.0%) experienced increased white blood cell and protein levels in the CSF after tofersen therapy, indicative of drug-related spinal cord and nerve root inflammation. Two of these patients (22.2%) demonstrated clinical symptoms and responded to steroid treatment. Three of the 27 patients (11.1%) that began treatment with tofersen died soon after starting treatment and were not included in the analyses.

Harms results were not provided in the Meyer et al. studies.

Critical Appraisal

The sponsor submitted data EAP cohort studies based on published reports; however, the absence of study protocols and statistical analysis plans limited the ability to fully assess the study design, outcome measurements, and analytical methods.

The analyses were primarily descriptive and unadjusted for confounders, reducing internal validity and limiting the ability to infer treatment effects. Additionally, the lack of a comparator group makes it difficult to separate treatment effects from natural disease progression or external influences.

The lack of blinding, in which both patients and clinicians were aware of the treatment administered, raises the potential for performance and detection biases, particularly in subjective measures such as ALSFRS-R score and AE reporting.

The EAP studies were affected by small sample sizes (fewer than 50 patients; only 6 in each of 2 studies), missing or incomplete data, and inconsistent reporting of outcomes, all of which undermine the reliability of progression slope estimates. For example, in the Italian study, 27 of 42 enrolled patients received treatment; 17 (40.5%) of whom had evaluable data. This substantial attrition raises the risk of survivor bias, as observed effects may reflect characteristics of a selected subgroup rather than true treatment effectiveness.

ALSFRS-R score slope estimates were based on 2 time points and assumed linear disease progression, which may not accurately reflect the typically nonlinear course of ALS. Therefore, these estimates may misrepresent true disease progression. The reliance on patient recall for prebaseline data introduces uncertainty, as recall bias may lead to inaccurate reporting of disease onset and prior ALSFRS-R score trajectory. In the Wiesenfarth et al. study, it was unclear whether observed ALSFRS-R score changes reflected treatment response or were confounded by the short follow-up duration. Likewise, it is unclear whether any improvements in ALSFRS-R scores would be sustained over a longer period, particularly in the context of the non–rapidly progressing disease targeted by the trial’s enrichment strategy.

Although post-treatment reductions in ALSFRS-R score decline were observed, the lack of a comparator group, small sample sizes, missing data, potential for bias (particularly from confounding), and reliance on slopes of ALSFRS-R scores from few time points reduced certainty in the results from these studies regarding the effectiveness of tofersen.

The EAP studies were conducted in small patient cohorts in Germany and Italy, limiting confidence in the generalizability of the findings to the ALS population in Canada. Given the limited reporting of baseline characteristics and small sample sizes, it is unclear whether these study populations reflect the diversity and clinical profiles of patients in Canada.

While the clinical experts consulted agreed that any trained clinician could administer the treatment under review, they emphasized that patients should remain under the care of an ALS specialist. The experts noted that access to multidisciplinary ALS care is more readily available to patients near more densely populated urban areas in Canada. Although efforts have been made to expand access in remote areas through telehealth and transport to specialized clinics, significant barriers to equitable care remain. As such, the centralized care settings in the reviewed studies may not fully reflect the realities of care delivery across Canada’s geographically dispersed health systems.

Ethical Considerations

Patient group, clinician group, clinical expert, drug program input, and relevant literature were reviewed to identify ethical and equity considerations associated with the use of tofersen to treat adults with *SOD1* ALS.

- Diagnosis, treatment, and experiences of ALS:** The initial time to diagnosis is lengthy given the lack of an ALS diagnostic marker, frequent misdiagnosis, and delayed referrals to neurologists. Diagnosing *SOD1* ALS is associated with additional challenges, including geographic disparities in access to genetic testing, delayed access to pretesting genetic counselling, and the existence of *SOD1* mutations of undetermined significance. Current treatments offer modest benefits and do not treat *SOD1* ALS specifically. Patients who have ALS and their caregivers experience physical, emotional, and financial burdens associated with the disease. Patients typically have progressive difficulty with mobility, speech, swallowing, performing tasks of daily living, and breathing. Patients and caregivers can experience profound distress, fear, and anxiety associated with disease progression, loss of independence, and the impacts of ALS on family members. Patients and caregivers also incur expenses associated with purchasing medical equipment, formal care support, travel, and home modifications, and often lose their income as they are unable to work.
- Clinical and economic evidence used in the evaluation of tofersen:** The pivotal phase III VALOR trial failed to meet its primary efficacy end point, and although there were meaningful differences in the 2 biomarkers used as secondary end points, their clinical meaningfulness is unvalidated. No studies have assessed tofersen's comparative effectiveness relative to the current standard of care, and, although the OLE study and the findings from the EAP studies suggested trends toward slowed disease progression, significant methodological limitations temper confidence in their findings. Further, several patient groups that likely would be encountered in clinical practice in Canada were underrepresented or excluded from the trial populations, including older patients, patients from racialized groups, patients diagnosed with slower-progressing *SOD1* ALS mutations, and patients with more medically complex needs. Collectively, the clinical uncertainties associated with the evaluation of tofersen complicates decision-making by patients, clinicians, and health systems. These uncertainties are heightened for groups that were underrepresented or excluded from the trial populations.
- Clinical use and implementation of tofersen:** Treatment with tofersen also will entail several access challenges as it must be prescribed and monitored by ALS specialists in tertiary care centres mainly located in large urban centres. Although access could be improved if patients received their monthly intrathecal injections in local settings, some patients would continue to experience access challenges. The use of tofersen may pose novel risks for patients as compared to the current standard of care, including serious neurologic AEs and risks associated with its intrathecal mode of delivery. Patients living with ALS and their caregivers, as well as clinicians, hold enhanced expectations and hopes for disease-modifying therapies as current treatments offer only modest benefits. These expectations, and the ongoing unmet needs of patients with ALS, should be accounted for when considering the potential benefits, harms, and evidentiary uncertainties associated with tofersen.

- **Health systems:** The introduction of tofersen may pose health resource utilization and system integration challenges, especially due to the resource-intensive nature of intrathecal delivery and the need to monitor and manage SAEs. The introduction of tofersen may require ongoing data collection and postmarket evaluation, as well as the development of a genetic testing infrastructure to support ongoing delivery and monitoring.

Economic Evidence

- Tofersen is available as 100 mg/15 mL vials for intrathecal injection. At the submitted price of \$28,370.68 per vial, the annual cost of tofersen is expected to be \$425,560 per patient in the first year of treatment and \$368,819 in subsequent years, based on the Health Canada–recommended dosage.
- Comparative clinical efficacy in the economic analysis was derived from the VALOR (part C) trial, which compared tofersen to placebo. Evidence submitted by the sponsor indicates that tofersen may result in little or no clinically meaningful difference compared to placebo for change in ALSFRS-R score.
- The results of the CDA-AMC base case suggest:
 - Tofersen plus background therapy will be associated with higher costs to the health care system than background therapy alone (incremental costs = \$1,205,885), primarily driven by the increased costs associated with tofersen.
 - Tofersen plus background therapy will be associated with a gain of 1.93 life-years compared to background therapy alone. When the impact on HRQoL is also considered, tofersen plus background therapy may result in a gain of 0.76 QALYs compared to background therapy alone.
 - The ICER of tofersen plus background therapy compared to background therapy alone was \$1,586,423 per QALY gained. The estimated ICER is highly uncertain because of the uncertainty in the comparative efficacy, economic model structure, and assumptions used in the sponsor's societal analysis.
 - Given the identified limitations with the submitted model structure, the economic analysis may not accurately assess the impact on patient health and health care resources. Thus, the cost-effectiveness estimates are highly uncertain.
- Results from both the sponsor and CDA-AMC analyses suggest that, with substantial price reductions (i.e., 90%), the ICER for tofersen plus background therapy remains above \$250,000 per QALY gained. There are 2 reasons for this result — it is partly due to more nondrug-related costs associated with tofersen plus background therapy and partly due to the predicted improvement in life expectancy associated with tofersen, which results in both additional drug acquisition costs and nondrug-related costs (i.e., drug administration, monitoring, and management of side effects) during this prolonged survival time. Even if the drug acquisition cost of tofersen is substantially lowered, there will still be high costs to the health care system as tofersen treatment is associated with background therapy

costs and costs pertaining to drug administration, monitoring, and management of side effects (approximately \$51,000).

- The sponsor submitted a base-case analysis conducted from the societal perspective. Due to the lack of robust evidence to support this approach, CDA-AMC was unable to consider a societal perspective.
- CDA-AMC estimates that the budget impact of reimbursing tofersen plus background therapy for the treatment of adults with *SOD1* ALS will be approximately \$36,169,911 over the first 3 years of reimbursement compared to the amount currently spent on background therapy alone, with an estimated expenditure of \$37,446,934 on tofersen over this period. The actual budget impact of reimbursing tofersen will depend on the number of people eligible for treatment.
- While genetic testing for *SOD1* mutations is currently performed as standard of care for patients with ALS, clinical expert feedback received by CDA-AMC indicated that there are access differences across jurisdictions that may impact the feasibility of accessing tofersen. The budget impact assumes all patients receive genetic testing; however, if there are access issues associated with genetic testing, the budget impact may be overestimated.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for tofersen for the treatment of adults with ALS associated with a mutation in the *SOD1* gene. In their request, the sponsor identified the following issue:

- The concomitant use of tofersen and edaravone should be allowed.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with ALS
- feedback on the draft recommendation from 2 patient groups, the ALS Society of Canada and ALS Action Canada
- feedback on the draft recommendation from 1 clinician groups, CALS
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed

Meeting date: July 23, 2025

Regrets: Four expert committee members did not attend.

Conflicts of interest: None

Minor reconsideration CDEC subpanel meeting date: November 07, 2025



Canada's Drug Agency
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Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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