PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **QALSODY™**

tofersen injection

Solution, 100 mg / 15 mL (6.7 mg/mL), for intrathecal use

Other nervous system drugs

QALSODY, indicated for:

- the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for QALSODY please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

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1 INDICATIONS

QALSODY (tofersen injection) is indicated for:

- The treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

The clinical benefit of QALSODY for the indication remains to be confirmed as this indication is issued market authorization with conditions. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Experience with the use of QALSODY in the geriatric population is limited. Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness, however a greater sensitivity in some older individuals cannot be ruled out. (see 7.1.4 Special Populations, Geriatrics).

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2 CONTRAINDICATIONS

QALSODY is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 0

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

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4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose of QALSODY is 100 mg (15 mL).
- QALSODY treatment should be initiated with three (3) loading doses administered at 14-day intervals (Day 0, Day 14, Day 28).
- A maintenance dose should be administered every 28 days thereafter (Day 56, Day 84, etc.).

Pediatric

Health Canada has not authorized an indication for pediatric use. Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatrics

There is no evidence for special dosage considerations based on age when QALSODY is administered

(see 7.1.4 Special Populations, Geriatrics).

Renal Impairment

QALSODY has not been studied in patients with renal impairment.

Hepatic Impairment

QALSODY has not been studied in patients with hepatic impairment (see 10.3 Pharmacokinetics).

4.4 Administration

QALSODY is administered intrathecally by healthcare professionals experienced in performing lumbar punctures. Aseptic technique must be used when preparing and administering QALSODY intrathecally (see 7 WARNINGS AND PRECAUTIONS, General).

Preparation

Vial preparation instructions:

- Prior to administration, the refrigerated vial should be allowed to warm to room temperature (25°C) without external heat sources (see 11 STORAGE, STABILITY AND DISPOSAL).
- The vial containing QALSODY should not be shaken.
- The solution should be visually inspected prior to removal of QALSODY from the vial. The solution should be free of visible particles. Only clear and colorless to slightly yellow solution should be administered. If not, the vial must not be used.

Procedural preparation instructions

- If indicated by the clinical condition of the patient, sedation can be considered.
- If indicated by the clinical condition of the patient, imaging to guide intrathecal administration of QALSODY can be considered.
- An unopened vial can be returned to the refrigerator for total time permitted (see 11 STORAGE, STABILITY AND DISPOSAL).
- Patients should be evaluated prior to and after intrathecal injection for the presence of potential conditions related to lumbar puncture to avoid serious procedural complications.

Administration

- Just prior to administration, the plastic cap should be removed from the vial and a non-spinal anesthesia needle attached to the syringe for the purpose of withdrawing tofersen from the vial. The syringe needle is inserted into the vial through the center of the over-seal to withdraw the required dose of 15 mL (equivalent to 100 mg) from the vial.
    - QALSODY must not be diluted.
    - External filters are not required.
- It is recommended that approximately 10 mL of cerebrospinal spinal fluid (CSF) is removed using a lumbar puncture needle prior to administration of QALSODY.
- QALSODY is administered as an intrathecal bolus injection using a lumbar puncture needle over 1 to 3 minutes.

- QALSODY contains no preservatives (see 11 STORAGE, STABILITY AND DISPOSAL).

- Any unused content of the single-dose vial should be discarded.

Following injection, no additional monitoring procedures are recommended apart from standard post-lumbar-puncture care.

4.5 Missed Dose

If the second loading dose is delayed or missed, QALSODY should be administered as soon as possible, and the third loading dose should be administered 14 days later.

If the third loading dose is delayed or missed, QALSODY should be administered as soon as possible, and the first maintenance dose should be administered 28 days later.

If a maintenance dose is delayed or missed, QALSODY should be administered as soon as possible. Subsequent maintenance doses should be administered every 28 days from the last dose.

5 OVERDOSAGE

No cases of overdose associated with QALSODY were reported in clinical trials.

In the event of overdose, medical care should be provided including consulting with a healthcare professional and close observation of the clinical status of the patient.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intrathecal	Solution, 100 mg / 15 mL	calcium chloride dihydrate, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium phosphate dibasic anhydrous, sodium phosphate monobasic dihydrate, water for injection

QALSODY is a sterile, clear and colorless to slightly yellow solution supplied as a 100 mg/15 mL (6.7 mg/mL) solution in a single-dose glass vial with stopper not made with natural rubber latex, and an aluminum over-seal with flip-off plastic button.

QALSODY is available in a pack of 1 vial.

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7 WARNINGS AND PRECAUTIONS

General

QALSODY should be administered by healthcare professionals who are experienced in performing lumbar puncture procedures. Patients should be evaluated for the presence of potential contraindications for lumbar puncture (e.g., skin infection near site of lumbar puncture, suspicion of increased intracranial pressure, uncorrected coagulopathy, acute spinal cord trauma), and all necessary precautions should be taken to avoid serious procedural complications.

Adverse reactions associated with the administration of QALSODY by lumbar puncture have been observed, including headache, back pain, post lumbar puncture syndrome, and infection (see 8 ADVERSE REACTIONS).

Driving and Operating Machinery

Studies on the effects on the ability to drive or use machines during treatment with QALSODY have not been performed.

Patients who develop visual disturbance during QALSODY use should be cautioned to avoid driving or operating machinery.

Hematologic

Coagulation abnormalities and acute severe thrombocytopenia have been observed after subcutaneously and intravenous administration of antisense oligonucleotides. If clinically indicated, platelet and coagulation laboratory testing is recommended prior to lumbar puncture procedure.

Neurologic

Aseptic or chemical meningitis

Serious adverse reactions of aseptic or chemical meningitis have been reported in patients treated with QALSODY. In clinical trials, two patients treated with QALSODY reported serious adverse event of aseptic or chemical meningitis (1.4%). Both patients were symptomatic and received 5 and 7 doses of QALSODY respectively before the onset of aseptic or chemical meningitis. One patient discontinued QALSODY. If symptoms consistent with aseptic or chemical meningitis develop, diagnostic evaluation and treatment should be initiated according to the standard of care.

Myelitis and/or radiculitis

Serious events of myelitis and radiculitis have been reported in patients treated with tofersen.

In the clinical studies, four patients receiving QALSODY 100 mg reported serious adverse reactions of myelitis (2.7%). The number of QALSODY doses received before the onset of myelitis ranged from 5 to 15 doses. Two patients were symptomatic. All four patients had abnormal magnetic resonance imaging (MRI) findings related to the event. Two patients discontinued treatment, with resolution of the event. Two patients required immunomodulatory treatment.

Two patients receiving QALSODY 100 mg reported serious adverse reactions of radiculitis (1.4%) after receiving 1 dose and 24 doses, respectively. Both adverse reactions were symptomatic. One patient had abnormal MRI findings related to the event. No patients discontinued treatment. One patient had sequelae of bilateral foot sensory loss.

If symptoms consistent with these adverse reactions develop, diagnostic evaluation and treatment

should be initiated according to the standard of care.

Increased intracranial pressure (ICP) and/or papilledema

Serious events of elevated intracranial pressure and/or papilledema in clinical studies were reported by four QALSODY-treated patients (2.7%). The number of QALSODY doses received before the onset of increased ICP and/or papilledema ranged from 7 to 18. All four adverse reactions were symptomatic. All patients had an MRI with no findings pertinent to the event. Management included long-term treatment with acetazolamide in several patients, and IV methylprednisolone with tofersen dosing in one patient. One adverse reaction led to permanent discontinuation of QALSODY, and one adverse reaction led to interruption of QALSODY treatment.

If symptoms consistent with these adverse reactions develop, diagnostic evaluation and treatment should be initiated according to the standard of care.

Renal

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after subcutaneous and intravenous administration of antisense oligonucleotides. If clinically indicated, urine protein testing is recommended. For persistent elevated urinary protein, further evaluation should be considered.

Reproductive Health: Female and Male Potential

- **Fertility**

  There are no data available on the potential effects on fertility in humans. In toxicity studies in animals, no effects on male or female fertility were observed (see 7.1.1 Pregnant Women and 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from clinical trials on the use of tofersen during pregnancy. Administration of tofersen in mice and rabbits had no impact on fertility, embryo-fetal development, or pre/postnatal development (see 16 NON-CLINICAL TOXICOLOGY).

Tofersen is not recommended during pregnancy and in patients of childbearing potential not using contraception.

7.1.2 Breastfeeding

There are no data on the use of QALSODY during lactation in humans. It is unknown whether tofersen or its metabolites are excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. A risk to the newborn or infants cannot be excluded. Tofersen is not recommended during breastfeeding. In rodent studies, tofersen was detected in milk samples from all tofersen-dosed animals. There were no tofersen-related effects on either the maternal dams or offspring (see 16 NON-CLINICAL TOXICOLOGY).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): QALSODY is not indicated for pediatric use. Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): A total of 13.5% (22/162) SOD1-ALS patients were 65 years of age and older and 1.2% (2/162) patients were 75 years of age and older at initiation of treatment in clinical trials. Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness. Data are limited, and a greater sensitivity of some older individuals cannot be ruled out.

NOC/c

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of QALSODY 100 mg was evaluated in 147 SOD1-ALS patients. The median patient exposure was 119.4 weeks (range 4 to 212 weeks). QALSODY was evaluated in the placebo-controlled Study 1 and in the open label extension Study 2.

Very common adverse reactions (≥ 10%) reported in QALSODY-treated patients were pain (66.0%), arthralgia (34.0%), fatigue (28.6%), CSF white blood cell increased (26.5%), CSF protein increased (26.5%), myalgia (19.0%), and pyrexia (18.4%).

A total of 12 serious neuroinflammatory adverse reactions were reported in 10 (7%) tofersen-treated patients in clinical trials.

The serious adverse reactions in tofersen-treated patients were myelitis (2.7%), increased intracranial pressure and/or papilledema (2.7%), radiculitis (1.4%) and aseptic or chemical meningitis (1.4%).

Serious neuroinflammatory reactions that led to discontinuation of tofersen included two cases of myelitis, one case each of aseptic meningitis and intracranial pressure increased.

Serious neuroinflammatory reactions that led to dose interruption included one case each of myelitis, papilledema, and intracranial pressure increased.

No cases lead to dose reduction, and none were fatal. The symptoms of the serious neuroinflammatory reactions were variable and resolved between 2-854 days after onset. These adverse reactions persisted for an average of 159 days.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 – Adverse Drug Reactions (ADRs) with an Incidence of ≥ 1% in Tofersen-Treated Patients in Study 1 (placebo-controlled study) and Study 2 (open-label study)

	Study 1 Part C		Study 1 and Study 2
	QALSODY 100 mg n = 72 N (%)	Placebo n = 36 N (%)	QALSODY 100 mg n = 147 N (%)
General disorders and administration site conditions			
Pain [1]	30 (41.7)	8 (22.2)	97 (66.0)
Fatigue	12 (16.7)	2 (5.6)	42 (28.6)
Pyrexia	3 (4.2)	1 (2.8)	27 (18.4)
Musculoskeletal and connective tissue disorders			
Arthralgia	10 (13.9)	2 (5.6)	50 (34.0)
Myalgia	10 (13.9)	2 (5.6)	28 (19.0)
Musculoskeletal stiffness	4 (5.6)	0 (0)	10 (6.8)
Nervous system disorders			
CSF white blood cell increased [2]	10 (13.9)	0 (0)	39 (26.5)
CSF protein increased	6 (8.3)	1 (2.8)	39 (26.5)
Intracranial pressure increased	0 (0)	0 (0)	6 (4.1)
Papilledema	0 (0)	0 (0)	5 (3.4)
Neuralgia	4 (5.6)	0 (0)	7 (4.8)
Aseptic Meningitis [3]	1 (1.4)	0 (0)	6 (4.1)
Radiculitis [4]	1 (1.4)	0 (0)	4 (2.7)
Myelitis [5]	2 (2.8)	0 (0)	4 (2.7)

[1] Pain includes preferred terms of pain, back pain, and pain in extremity.

[2] CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis.

[3] Aseptic meningitis includes preferred terms of meningitis chemical and meningitis aseptic.

[4] Radiculitis includes preferred terms of radiculopathy and lumbar radiculopathy.

[5] Myelitis includes preferred term of myelitis, myelitis transverse, and neurosarcoidosis.

Note: Table 2 represents cases of serious and non-serious ADRs.

Selected adverse events

See 7 WARNINGS AND PRECAUTIONS for descriptions of the following selected adverse events:

Myelitis and/or radiculitis
Increased intracranial pressure and/or papilledema
Aseptic or chemical meningitis

8.3 Less Common Clinical Trial Adverse Reactions

There are no less common clinical trial adverse reactions, with incidence of < 1%, for tofersen.

8.4 Abnormal laboratory findings: hematologic, clinical chemistry and other quantitative data

Elevated cerebrospinal fluid (CSF) white blood cell (WBC) and protein levels were reported commonly both as non-serious adverse drug reactions (ADRs) and as abnormal laboratory findings. The incidence of CSF WBC and CSF protein increased ADRs was higher in the tofersen-treated vs placebo-treated patients in Study 101 Part C. In addition, data from non-clinical studies, the pro-inflammatory nature of ASOs, and the relation to irritation or inflammation locally or systemically, indicate a likely causal relationship to QALSODY.

These findings were also reported in association with the common neuro inflammatory ADRs associated with tofersen use. Clinical significance of these findings is unknown.

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Clinical drug interaction studies have not been performed.

The co-administration of other intrathecal medicinal products with tofersen has not been evaluated and the safety of these combinations is not known.

In *in vitro* studies, tofersen was not found to be a substrate for, or an inducer or inhibitor of CYP450-mediated oxidative metabolism; therefore, it should not interfere with other medicinal products that interact with these metabolic pathways.

In vitro studies indicated that the likelihood for interactions with tofersen due to competition with or inhibition of transporters is low. Tofersen is not a substrate of BCRP and MDR1 efflux or MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 SLC transporters, nor is it an inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 SLC, BCRP, BSEP, or MDR1 transporters.

NOC/c

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The human SOD1 gene encodes an abundant dimeric enzyme, copper/zinc superoxide dismutase (Cu/ZnSOD or SOD1), which catalyzes the transmutation of superoxide (O_2^-) into oxygen (O_2) and hydrogen peroxide (H_2O_2). In SOD1-ALS patients, mutations in the SOD1 gene lead to accumulation of a toxic form of SOD1 protein, resulting in axonal injury and neurodegeneration. Tofersen is an antisense oligonucleotide that is complementary to a portion of the 3' untranslated region (3'UTR) of the mRNA for human SOD1 and binds to the mRNA by Watson-Crick base pairing (hybridization). This hybridization of tofersen to the cognate mRNA results in RNase-H-mediated degradation of the mRNA for SOD1, which reduces the amount of SOD1 protein synthesis.

10.2 Pharmacodynamics

See 14 CLINICAL TRIALS for data related to SOD1 proteins (as an indirect measure of target engagement) and neurofilaments (biomarker of axonal injury and neurodegeneration).

Cardiac Electrophysiology

There was no clinical or non-clinical evidence that tofersen would prolong the QTc interval.

No thorough QT (TQT) prolongation study has been conducted but concentration-QTc analyses and electrocardiogram (ECG) monitoring were completed in the clinical trials. ECG measurements and the values for the tofersen 100 mg group (n = 41) were similar to the placebo group (n = 34) in Study 1 part C. The incidence of abnormalities in ECG measurements was higher in the tofersen group compared to the placebo group, with 8 patients (11.3%) displaying a maximum increase from baseline in Fridericia formula (QTcF) > 30 to 60 ms in the tofersen group compared to 2 patients (5.6%) in the placebo group. No patients in the tofersen or placebo group displayed an increase from baseline in QTcF > 60 ms, and no patients displayed maximum postbaseline QTcF > 480 ms.

Tofersen demonstrated a very low potential for cardiac IKR (hERG channel) inhibition (IC_{50} > 34 µM) and did not produce adverse effects in cardiovascular safety pharmacology endpoints in nonhuman primates at the highest dose tested (35 mg).

10.3 Pharmacokinetics

The single and multidose pharmacokinetics of tofersen, administered via intrathecal injection, were characterized in plasma and CSF of adult ALS patients with a SOD1 mutation and in autopsy tissue from deceased clinical trial patients (n=3).

Table 3 – Summary of Tofersen Plasma Pharmacokinetic Parameters in adult patient population

	C_{max}	T_{max}[1]	$t_{½}$	AUC_{0-24h}	CL[2]	Central Vd[2]
Single dose mean	1.414 mg/L (79.5% CV)	3 h (1-24 h)	Not estimated	13.663 mg.h/L (58.1% CV)	8.32 L/h	56.6

[1] Median (Range)

[2] Population PK model estimates

Absorption

The maximum CSF trough concentration occurred at the third dose, which was the last dose of the loading period. There was little to no accumulation with monthly dosing after the loading phase. Tofersen is transferred from the CSF into the systemic circulation, with a median time to maximum concentration (T_{max}) plasma values ranging from 2 to 6 hours post IT administration. There was no accumulation in plasma exposure measures (C_{max} and AUC) after monthly maintenance dosing.

Distribution

Autopsy tissue from tofersen-treated patients (n = 3) showed that tofersen administered intrathecally was distributed within the central nervous system (CNS) and spinal cord tissues.

Metabolism

Tofersen is metabolized predominantly through exonuclease (3' and 5')-mediated hydrolysis and is not a substrate for, inhibitor, or inducer of CYP450 enzymes.

Elimination

The primary route of elimination is expected via urinary excretion of unchanged tofersen and its metabolites. Although CNS tissue half-life cannot be measured in humans, the mean terminal elimination half-life was measured in the CNS tissue of cynomolgus monkeys and found to be 31 to 40 days.

Immunogenicity

The immunogenic response to tofersen was evaluated in 166 patients with post-baseline plasma samples for anti-drug antibodies (ADAs). Overall, 97 tofersen-treated patients (58.4%) developed treatment-emergent ADAs, of which 14 patients had a transient ADA response and 83 patients had a persistent ADA response. Though data are limited, no discernible effects of ADAs on efficacy or safety (incidence of AEs including hypersensitivity, anaphylactic reaction, and angioedema) have been observed. Medical review of individual cases of serious neurological events also showed no association with ADA status.

The presence of ADAs appeared to decrease plasma clearance by 32%. The impact of ADAs was evaluated but was not identified as a significant covariate for either the SOD1 protein or NfL PKPD models.

Special Populations and Conditions

- **Pediatrics**

  The pharmacokinetics of tofersen in pediatric patients has not been studied.

- **Geriatrics**

  Of the 166 patients who received tofersen in clinical trials, a total of 22 patients were 65 years of age and older, including 2 patients 75 years of age and older. No overall differences in clinical PK were observed between these patients, however data are limited.

- **Sex**

  Population pharmacokinetic analysis shows that sex of the patient does not affect the pharmacokinetics of tofersen.

- **Ethnic Origin**

  Most patients were Caucasian (61% of total), undisclosed (30% of total) or Japanese (6.5% of total). A total of 7 Japanese patients were enrolled in Study 1 part C and 3 of these patients received tofersen 100 mg. The mean (min, max) of $AUC_{0\text{-}24}$ and C_{max} in Japanese patients after the first dose of tofersen 100 mg were 6992.0 (4242, 15040) h*ng/mL and 462.3 (227, 1435) ng/mL, respectively. These values were within the ranges of overall population.

- **Hepatic Insufficiency**

  The pharmacokinetics of tofersen in patients with hepatic impairment has not been studied. Tofersen is not expected to undergo metabolism by hepatic enzymes.

- **Renal Insufficiency**

  The pharmacokinetics of tofersen in patients with renal impairment has not been studied.

  Plasma Protein Binding

  Tofersen is highly bound to human plasma proteins (≥ 98% bound) at clinically relevant or

higher plasma concentrations (0.1 and 3 mcg/mL), which limits glomerular filtration and reduces urinary excretion of the drug. The likelihood of drug-drug interactions due to competition with plasma protein binding is very low.

- **Body Weight**

  Baseline body weight did not significantly influence tofersen PK parameters such as CSF volume, plasma volume, and clearance. However, body surface area (BSA), an alternative measure of body size, was identified as a covariate of plasma clearance of tofersen. Although BSA influences plasma volume and clearance of tofersen, the plasma exposure is relatively low. Given that the CSF exposure is similar over the entire range of body weight as well as the target tissues being located within the CNS, no dose adjustments are required for BSA.

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated at 2°C to 8°C in the original package to protect from light. Do not freeze.

The vial of QALSODY, in its original carton to protect from light, can be stored for up to 14 days at room temperature (not to exceed 30°C).

If removed from the original carton, the unopened vial of QALSODY can be removed from and returned to the refrigerator, if necessary, for not more than 6 hours per day at room temperature (not to exceed 30°C) for a maximum of 6 days (36 hours).

Once drawn from the vial, the solution is physically and chemically stable in syringes with polypropylene barrel at room temperature (15°C to 30°C) for up to 4 hours before administration; otherwise, it must be discarded.

12 SPECIAL HANDLING INSTRUCTIONS

For single dose only.

Discard any unused solution left in a vial. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

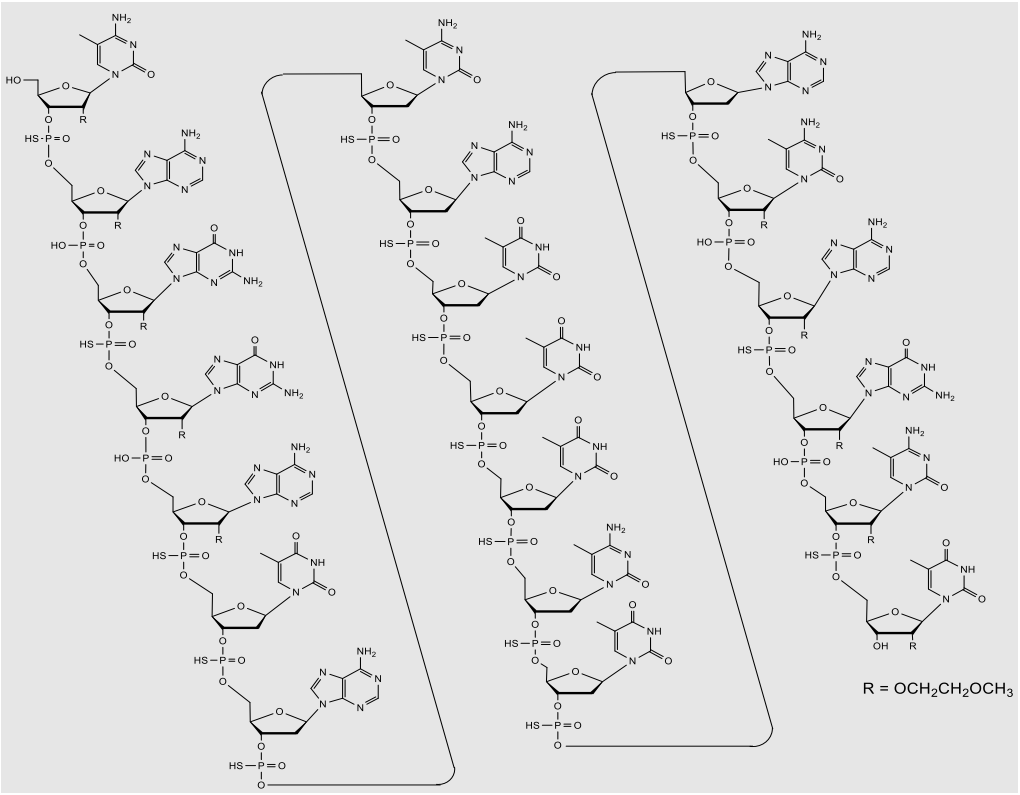
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name:	tofersen
Chemical name:	Tofersen is a 20-base residue (20-mer) 5-10-5 methoxyethyl (MOE) gapmer mixed backbone oligonucleotide. Of the nineteen internucleotide linkages, fifteen are 3′-O to 5′-O phosphorothioate diesters, and four are 3′-O to 5′-O phosphate diesters. Ten of the twenty sugar residues are 2′-deoxy-D-ribose and the remainder are 2′-O-(2-methoxyethyl)-D-ribose. The residues are arranged so that there are five MOE nucleosides at the 5′ and 3′-ends of the molecule flanking a gap of ten 2′-deoxynucleosides. The cytosine and uridine bases are methylated at the 5-position: 2′-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-adenylyl-(3′-O→5′-O)-2′-O-(2-methoxyethyl)-P-thioguanylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-guanylyl-(3′-O→5′-O)-2′-O-(2-methoxyethyl)-P-thioadenylyl-(3′-O→5′-O)-2′-deoxy-P-thiothymidylyl-(3′-O→5′-O)-2′-deoxy-P-thioadenylyl-(3′-O→5′-O) -2′-deoxy-5-methyl-P-thiocytidylyl-(3′-O→5′-O)-2′-deoxy-P-thioadenylyl-(3′-O→5′-O) -2′-deoxy-P-thiothymidylyl-(3′-O→5′-O)-2′-deoxy-P-thiothymidylyl-(3′-O→5′-O)-2′-deoxy-P-thiothymidylyl-(3′-O→5′-O)-2′-deoxy-5-methyl-P-thiocytidylyl-(3′-O→5′-O)-2′-deoxy-P-thiothymidylyl-(3′-O→5′-O)-2′-deoxy-P-thioadenylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-5-methylcytidylyl-(3′-O→5′-O)-2′-O-(2-methoxyethyl)-P-thioadenylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-guanylyl-(3′-O→5′-O)-2′-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3′-O→5′-O) -2′-O-(2-methoxyethyl)-5-methyluridine
Molecular formula and molecular mass:	$C_{230}H_{317}N_{72}O_{123}P_{19}S_{15}$ (free acid form), molecular mass: 7127.86 atomic mass units (amu)

Structural formula:



Physicochemical properties: pH of tofersen is approximately 7.2 in a buffered aqueous solution

NOC/c

14 CLINICAL TRIALS

Clinical Trials by Indication

SOD1 ALS

Table 4 – Summary of patient demographics for clinical trials in amyotrophic lateral sclerosis (ALS)

Study #	Study design	Dosage, route of administration	Study patients (n)	Mean age (Range)	Sex
Study 1	Randomized, double-blind, placebo-controlled study	**Part C:** Tofersen 100 mg, or placebo Intrathecal, 24 weeks	Tofersen: 72 Placebo: 36	49.8 years (23 – 78 years)	M: 62 (56%) F: 46 (44%)
Study 2	Open-label extension for Study 1 Part C patients (with a blinded loading dose period)	Tofersen 100 mg Intrathecal	Previous tofersen: 63 Previous placebo: 32	50.5 years (24 – 74 years)	M: 56 (59%) F: 39 (41%)

The efficacy of tofersen was assessed in a 28-week randomized, double-blind, placebo-controlled clinical trial (Study 1 part C) in patients aged 23 to 78 years with weakness attributable to ALS and a SOD1 mutation confirmed by central laboratory. One hundred eight (108) patients were randomized 2:1 to receive treatment with either tofersen 100 mg or placebo for 24 weeks (3 loading doses followed by 5 maintenance doses). Forty-two (42) unique SOD1 mutations were evaluated, with the most common being p.Ile114Thr (n = 20), p.Ala5Val (n = 17), p.Gly94Cys (n = 6), and p.His47Arg (n = 5). Concomitant riluzole and/or edaravone use was permitted for patients who were on a stable dose for at least 30 or 60 days prior to trial baseline, respectively.

At the end of Study 1 part C, 95/108 patients (tofersen 100 mg: n = 63; placebo: n = 32) had the option to enroll in Study 2, an open-label extension trial to assess long-term safety. In Study 2, all patients received tofersen 100 mg.

Baseline disease characteristics in the overall intent to treat (ITT) population were generally similar in the tofersen-treated patients and placebo-treated patients. At baseline, 62% of patients were taking riluzole, and 8% of patients were taking edaravone. Mean (SD) baseline ALSFRS-R score was 36.9 (5.9) in the QALSODY treatment group and 37.3 (5.8) in the placebo group. Median time from symptom onset was 11.4 months in the QALSODY treatment group and 14.6 months in the placebo group. Mean (SD) baseline plasma NfL levels were 100.4 (82.8) pg/mLin the QALSODY treatment group and 89.7 (86.5) pg/mL in the placebo group.

The prespecified primary analysis population (n = 60, modified intent to treat [mITT]) had a slow vital capacity (SVC) ≥ 65% of predicted value as adjusted for sex, age, and height (from the sitting position) at screening 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 SVC ≥ 50% of predicted value as adjusted for sex, age, and height (from the sitting position) at screening and did not meet the enrichment criteria for rapid disease progression.

Study Results

Study 1 part C:

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. The results numerically favored tofersen, however were not statistically significant (tofersen-placebo adjusted mean difference [95% CI]: 1.2 [-3.2, 5.5]).

Numerically larger differences were observed between tofersen and placebo over 28 weeks in patients with baseline NfL values above the median [mean difference (95% CI) 3.9, (-1.0;8.9)] compared to patients with baseline NfL values below the median [0.6, (-1.3,4.2)]. Clinical secondary outcomes did not reach statistical significance.

Secondary endpoints of change from baseline at Week 28 in plasma NfL, a biomarker of axonal injury and neurodegeneration, and CSF SOD1 protein, an indirect measure of target engagement, favored tofersen.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

In a repeat-dose toxicology study (9 months), intrathecal (IT) administration of tofersen to adult cynomolgus monkeys was generally well-tolerated. The exception was a female in the high dose group (35 mg; equivalent to 350 mg per IT injection in humans) that had behavior described as muscle cramping, head/neck dorsiflexion, and opisthotonos-like-back-arching posture after IT dosing. Electroencephalogram (EEG) indicated the absence of seizure. The no observed adverse effect levels (NOAELs) in the repeat dose chronic toxicology studies were 150 mg/kg subcutaneous administration in the mouse and 12 mg intrathecal administration in the 9-month nonhuman primate.

Using the nonhuman primate as the most sensitive species, a dose of 12 mg converts to the HED of 120 mg, based on monkey to human CSF volume scaling (approximately 10-fold between human and monkeys), which provides a 1.2-fold safety margin to the MRHD of 100 mg. Based on plasma exposure (AUC_{0-24}) in nonhuman primates at 12 mg and humans at 100 mg, the exposure-based safety margin is approximately 2.2 times the MRHD of 100 mg.

Evidence of myelitis was not observed in the nonclinical toxicology studies for tofersen. However, vacuolation of neurons in brain and spinal cord as well as mononuclear cell infiltrates in spinal cord/nerve roots were seen with tofersen as well as with other antisense oligonucleotides (ASOs). None of these findings were associated with degenerative changes in the brain or spinal cord.

Genotoxicity:

Tofersen demonstrated no evidence of mutagenicity based on nonclinical genotoxicity studies (in vitro Ames bacterial mutagenicity, in vitro chromosome aberration, and in vivo mouse micronucleus assays).

Carcinogenicity:

Carcinogenicity studies with tofersen have not been performed.

Reproductive and Developmental Toxicology:

Reproductive toxicology studies were conducted using subcutaneous administration of tofersen in mice and rabbits. No impact on fertility, embryo-fetal development, or pre/postnatal development was observed. Male mice in the high dose group of 30 mg/kg (> 50 times the human exposure [AUC] following 100 mg tofersen) had minimal to mild seminiferous tubular degeneration, seminiferous tubule dilatation, spermatid retention, apoptosis of epithelial cells, increased cellular debris in the testes, and hypospermia in the epididymis. In addition, an increase in prostate weight was also noted however, there were no tofersen-related adverse effects on mating and fertility or sperm parameters. In female mice, there was no tofersen-related mortality or early delivery and there were no effects on mating or fertility. In a perinatal/postnatal reproduction study in mice, there were no adverse effects

on the F0 females or on the growth and development of the F1 pups at the highest dose evaluated (30 mg/kg). Translation of mouse fertility data to humans is limited based on the lack of cross-reactivity of tofersen to SOD1 in rodents.

Microscopic evaluation of reproductive tissues from both males and females in the 13-week and 39-week non-human primates (NHP) toxicology studies revealed no effects on the reproductive tissues. There were no effects on embryo-fetal development in mice or rabbits. Female general toxicity and reproductive / developmental NOAEL for tofersen was 30 mg / kg / dose, the highest dose tested in mice and rabbits.

Tofersen was detected in mouse milk samples from all tofersen-dosed animals. There were no tofersen-related effects on either the maternal dams or offspring.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrQALSODY ™
tofersen injection

Read this carefully before you start receiving **QALSODY** and each time you receive an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **QALSODY**.

What is QALSODY used for?

For the following indication QALSODY has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- QALSODY is used to treat adults with a type of amyotrophic lateral sclerosis (ALS) caused by an altered superoxide dismutase 1 (SOD1) gene. This is a rare type of motor neuron disease.

What is a Notice of Compliance with Conditions (NOC/c)
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does QALSODY work?
ALS associated with an altered SOD1 gene causes a build-up of toxic SOD1 protein in the body. This causes loss of nerve cells in the brain and spine, leading to weakness in muscles, including those used for movement, breathing, and swallowing.

QALSODY contains the active substance tofersen. It belongs to a group of medicines known as antisense oligonucleotides. QALSODY works by reducing the amount of SOD1 protein produced. This may reduce the loss of nerve cells and slow down the loss of muscle strength and function.

What are the ingredients in QALSODY?
Medicinal ingredients: tofersen
Non-medicinal ingredients: calcium chloride dihydrate, sodium phosphate dibasic anhydrous, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium phosphate monobasic dihydrate, and water for injection

QALSODY comes in the following dosage forms:
Solution for intrathecal injection: 100 mg / 15 mL (6.7 mg / mL).

Do not use QALSODY if:

- You are allergic to tofersen or to any of the other ingredients in QALSODY.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given QALSODY. Talk about any health conditions or problems you may have, including if you:

- have inflamed skin or an infection at or near the proposed site of injection for QALSODY.
- have symptoms of increased pressure around the brain such as a headache that may become severe, accompanied with nausea, vomiting and/or vision problems.
- have a disease or condition affecting your blood's ability to coagulate.
- have a traumatic spinal cord injury.
- are pregnant, think you are pregnant, planning to become pregnant or could become pregnant and are not using an effective birth control method.
- are breastfeeding or planning to breastfeed.

Other warnings you should know about:

QALSODY may cause serious side effects associated with inflammation of the nervous system. These include:

- **Myelitis** (inflammation of the spinal cord)
- **Radiculitis** (inflamed nerve root)
- **Aseptic or chemical meningitis** (inflammation of the protective lining of the brain and spinal cord)
- **Increased intracranial pressure** (increased pressure around the brain). This can also lead to **papilledema** (swelling of the nerve that connects the eye to the brain).

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Pregnancy and breastfeeding:

- It is not known if QALSODY can harm an unborn baby. Therefore, QALSODY is not recommended during pregnancy and in patients able to get pregnant who are not using an effective birth control method.
- It is not known if QALSODY can pass into breast milk and harm a breastfed baby. Therefore. breastfeeding is not recommended during your treatment.

Driving and using machines: It is not known if QALSODY can affect your ability to drive or use machines. If you develop vision problems while taking QALSODY, you should not drive or use machinery.

Check-ups and testing: Your healthcare professional may do laboratory tests before starting and/or regularly during your treatment with QALSODY. They may perform:

- Blood tests to:
  - check the level of platelets in your blood; and
  - measure your blood's ability to clot and how long it takes.
- Urine tests to check the health of your kidneys.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with QALSODY:

No drug interaction studies have been performed.

How QALSODY is given:

- QALSODY is given by injection in the lower back. This injection:
  - is called a lumbar puncture and is done by inserting a needle in the space around the spinal cord (intrathecal). It should not be injected anywhere else or taken any other way.
  - will be given by a healthcare professional experienced in doing lumbar punctures and will be done in a healthcare setting.
- You may also be given a medicine to make you relax or sleep during the injection. Your healthcare professional may use imaging techniques to help with the administration of QALSODY if required.
- Your healthcare professional will tell you how long you need to keep receiving QALSODY. Don't stop treatment with QALSODY unless your healthcare professional tells you to.
- Ask your healthcare professional if you have any questions about how QALSODY is given.

Usual dose:

The recommended dose of QALSODY is 100 mg (15 mL). You will receive QALSODY based on the schedule below:

- The first 3 doses of QALSODY will be administered 14 days apart: on Day 0, Day 14 and Day 28 of your treatment.
- And once every 28 days thereafter: on Day 56, Day 84, etc.

Overdose:

If you think you, or a person you are caring for, have been given too much QALSODY, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss an appointment, contact your healthcare professional **right away** to let them know you missed your injection. Your healthcare professional will advise you when to come next for your scheduled appointment.

What are possible side effects from using QALSODY?

These are not all the possible side effects you may have when taking QALSODY. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with QALSODY may include:

- pain, including back pain and pain in your extremities
- muscle pain or stiffness
- joint pain
- nerve pain (including burning, stabbing and "pins and needles" sensations)
- lack of energy
- fever

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Papilledema (swelling of the nerve that connects the eye to the brain): vision changes such as blurred vision, double vision, flickering, or complete loss of vision. May be accompanied with headache, nausea or vomiting.		√	
Increased intracranial pressure (increased pressure around the brain): headache, nausea, vomiting. May be accompanied with vision problems.		√	
Aseptic or chemical meningitis (inflammation of the protective lining of the brain and spinal cord): fever, nausea, fatigue, sudden headache or stiffness of your neck, sensitivity to light, vomiting.		√	
Radiculitis (inflamed nerve root): pain that radiates along the path of the nerve, usually to the extremities, sensation of numbness, tingling or muscle weakness, neck or back pain.		√	
Myelitis (inflammation of the spinal cord): pain in the neck, back or head, weakness in arms or legs, tingling, numbness of the feet and legs, sharp pain that moves down your legs and arms or around your chest and abdomen, problems with bladder or bowel control.		√	
UNKNOWN FREQUENCY			
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Kidney toxicity (damage to the kidneys): back and abdominal pain, change in the colour of urine (pale or dark) decrease in amount of urine produced, pain or discomfort when urinating, swelling of the legs and ankles.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

QALSODY will be stored by your healthcare professional as follows:

- Refrigerated between 2°C to 8°C in the original carton to protect from light. Do not freeze.
- The vial in its original carton can be stored for up to 14 days at room temperature (not to exceed 30°C).
- If removed from the original carton, the unopened vial can be removed from and returned to the refrigerator, if necessary, for not more than 6 hours per day at room temperature (not to exceed 30°C) for a maximum of 6 days (36 hours).
- If not administered right away, the solution may be stored in a syringe with a polypropylene barrel at room temperature (15 - 30°C) for up to 4 hours. Otherwise, it must be discarded.

Keep this medicine out of the sight and reach of children.

If you want more information about QALSODY:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-

product-database.html); the manufacturer's (Biogen Canada Inc.) website www.biogen.ca/products/QALSODY_PM_EN.

This leaflet was prepared by Biogen Canada Inc.

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