

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Qalsody 100 mg solution for injection

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 15 ml vial contains 100 mg of tofersen.

Each ml contains 6.7 mg of tofersen.

### Excipient with known effect

Each 15 ml vial contains 52 mg of sodium.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Solution for injection

Clear and colourless to slightly yellow solution with a pH of 6.7 to 7.7.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Qalsody is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

### **4.2 Posology and method of administration**

Treatment with tofersen should only be initiated by a physician with experience in the management of ALS.

Qalsody should be administered by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

#### Posology

The recommended dose is 100 mg of tofersen per treatment.

Tofersen treatment should be initiated with 3 loading doses administered at 14-day intervals.

A maintenance dose should be administered once every 28 days thereafter.

#### *Missed or delayed doses*

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

#### *Duration of treatment*

The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy.

#### Special populations

##### *Elderly*

Experience with the use of tofersen in the elderly is limited. However, from the clinical data available, the efficacy and safety of tofersen are expected to be similar to that of other age groups studied. There is no evidence for special dose considerations based on age when tofersen is administered.

##### *Renal impairment*

Tofersen has not been studied in patients with renal impairment.

##### *Hepatic impairment*

Tofersen has not been studied in patients with hepatic impairment.

##### *Paediatric population*

The safety and efficacy of Qalsody in paediatric patients below the age of 18 years has not been established. No data are available.

#### Method of administration

Qalsody is for intrathecal use by lumbar puncture.

- It is recommended to ensure intrathecal access prior to removing the plastic cap from the vial and drawing up the tofersen dose.
- Just prior to administration, the plastic cap should be removed from the vial and a nonspinal 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 overseal to withdraw the required dose of 15 ml (equivalent to 100 mg) from the vial.
  - Qalsody must not be diluted.
  - External filters, including bacterial or particulate 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 tofersen.
- Tofersen is administered as an intrathecal bolus injection using a lumbar puncture needle over 1 to 3 minutes.

Procedural preparation instruction:

- 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 tofersen can be considered.
- Prior to removing the vial's cap on the aluminium overseal, readiness of the patient should be confirmed. An unopened vial can be returned to the refrigerator; for total time permitted, see section 6.3.
- 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.

Following injection, standard post-lumbar-puncture care is recommended.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Lumbar puncture procedure

There is a risk of adverse reactions occurring as part of the lumbar puncture procedure (e.g. headache, back pain, post lumbar puncture syndrome, infection).

#### Myelitis and/or radiculitis

Serious cases of myelitis and radiculitis have been reported in patients treated with tofersen. If symptoms consistent with these adverse reactions develop, diagnostic evaluation and treatment should be initiated according to the standard of care.

#### Increased intracranial pressure and/or papilloedema

Serious cases of increased intracranial pressure and/or papilloedema have been reported in patients treated with tofersen. If symptoms consistent with these adverse reactions develop, diagnostic evaluation and treatment should be initiated according to the standard of care.

#### Thrombocytopenia and coagulation abnormalities

Thrombocytopenia and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of subcutaneously or intravenously administered antisense oligonucleotides. If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of tofersen.

#### Renal toxicity

Renal toxicity has been observed after administration of subcutaneously and intravenously administered antisense oligonucleotides. If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.

#### Excipients

##### *Sodium*

This medicinal product contains 52 mg sodium in each 15 ml, equivalent to 3% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

##### *Potassium*

This medicinal product contains potassium, less than 1 mmol (39 mg) per 15 ml dose, i.e., essentially 'potassium-free'.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have 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.

Tofersen is not an inducer or inhibitor of CYP450-mediated oxidative metabolism; therefore, it should not interfere with other medicinal products that interact with these metabolic pathways.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are no data from the use of tofersen in pregnant women. Studies in animals in which tofersen is not pharmacologically active do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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

##### Breast-feeding

There are no data on the use of tofersen during breast-feeding in humans. Available pharmacodynamic data in animals have shown excretion of tofersen in milk (see section 5.3). A risk to the newborn/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tofersen therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

##### Fertility

There are no data available on the potential effects on fertility in humans. Toxicity studies in animals have indicated that tofersen would not appear to have harmful effects on male or female fertility (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Tofersen has minor influence on the ability to drive and use machines. Patients who develop visual disturbance under tofersen should be cautioned to avoid driving or operating machinery.

#### **4.8 Undesirable effects**

##### Summary of safety profile

The serious adverse reactions in tofersen-treated participants were myelitis (2.7%), increase intracranial pressure and/or papilloedema (2.7%), radiculitis (1.4%) and aseptic meningitis (1.4%). The most common adverse reactions reported in tofersen-treated participants were pain (66%), arthralgia (34%), fatigue (28.6%), CSF white blood cell increased (26.5%), CSF protein increased (26.5%), myalgia (19%) and pyrexia (18.4%).

##### Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and frequency using the following convention: Very Common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ); Rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ); Very Rare ( $< 1/10\ 000$ ); not known (cannot be estimated from the available data).

**Table 1: Adverse reactions with Qalsody-treated participants in Study 101 and Study 102**

System Organ Class (SOC)	Adverse reaction	Frequency
Nervous system disorders	CSF white blood cell increased*	Very common
	CSF protein increased	Very common
	Papilloedema‡	Common
	Neuralgia	Common
	Aseptic meningitis††	Common
	Radiculitis†	Common
	Myelitis§	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Musculoskeletal stiffness	Common
General disorders and administration site conditions	Pain‡‡	Very common
	Fatigue	Very common
	Pyrexia	Very common

\* CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis.

† Radiculitis includes preferred terms of radiculopathy and lumbar radiculopathy.

‡ Papilloedema includes preferred terms of papilloedema and intracranial pressure increased. See discussion in Description of selected adverse reactions (ARs).

§ Myelitis includes preferred terms of myelitis, myelitis transverse, and neurosarcoidosis. See discussion in Description of selected adverse reactions.

†† Aseptic meningitis includes preferred terms of meningitis chemical and meningitis aseptic. See discussion in Description of selected adverse reactions.

‡‡ Pain includes preferred terms of pain, back pain, and pain in extremity.

### Description of selected adverse reactions

#### *Lumbar puncture procedure*

Adverse reactions associated with the administration of tofersen by lumbar puncture have been observed. The adverse reactions commonly associated with lumbar puncture are headache, back pain, post lumbar puncture syndrome, infection. The incidence and severity of these events were consistent with events expected to occur with lumbar puncture.

#### *Myelitis and/or radiculitis*

In the clinical studies, 4 participants receiving tofersen 100 mg reported serious reactions of myelitis (2.7%). The number of tofersen doses received before the onset of myelitis ranged from 5 to 15 doses. Two participants were symptomatic and 2 participants were asymptomatic. All 4 participants had abnormal magnetic resonance imaging (MRI) findings related to the event. Two participants discontinued treatment, and the event resolved. In the remaining 2 participants, the event did not lead to discontinuation of treatment (see section 4.4).

Two participants receiving tofersen 100 mg reported serious reactions of radiculitis (1.4%). The number of tofersen doses received before the onset of radiculitis ranged from 1 to 24 doses. Both reactions were symptomatic. One participant had abnormal MRI findings related to the event and one participant had a normal MRI. No participants discontinued treatment, and the reactions resolved with sequelae in one and without sequelae in the second participant (see section 4.4).

#### *Increased intracranial pressure and/or papilloedema*

Four participants receiving tofersen 100 mg reported serious reactions of increased intracranial pressure and/or papilloedema (2.7%). The number of tofersen doses received before the onset of increased intracranial pressure and/or papilloedema ranged from 7 to 18 doses. All 4 reactions of increased intracranial pressure and/or papilloedema were symptomatic. Four participants had an MRI with no findings pertinent to the event. One reaction finally led to permanent discontinuation of tofersen, one reaction led to interruption of tofersen treatment. All reactions were manageable with standard of care (see section 4.4).

#### *Aseptic or chemical meningitis*

Two participants receiving tofersen 100 mg reported serious reactions of aseptic or chemical meningitis (1.4%). The number of tofersen doses received before the onset of aseptic or chemical meningitis ranged from 5 to 7 doses. Both reactions of aseptic or chemical meningitis were symptomatic. One participant had an MRI with no findings pertinent to the event. One participant discontinued tofersen, and the other participant did not.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

No cases of overdose associated with tofersen were reported in clinical studies.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other nervous system drugs, ATC code: **N07XX22**

SOD1-ALS is a primarily autosomal-dominant disorder affecting approximately 2% of the ALS population. Mutations in the SOD1 gene lead to accumulation of a toxic form of SOD1 protein. Over 200 unique SOD1 mutations associated with ALS have been identified with a median disease duration of approximately 2.3 years.

#### Mechanism of action

The human SOD1 gene encodes an abundant dimeric enzyme, copper/zinc superoxide dismutase (Cu/ZnSOD or SOD1), which catalyses 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 (ASO) 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 (hybridisation). This hybridisation 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.

#### Pharmacodynamic effects

##### *Total CSF SOD1 protein*

Total CSF SOD1 was measured in Studies 101 Part C (VALOR) and 102 as an indirect measure of target engagement.

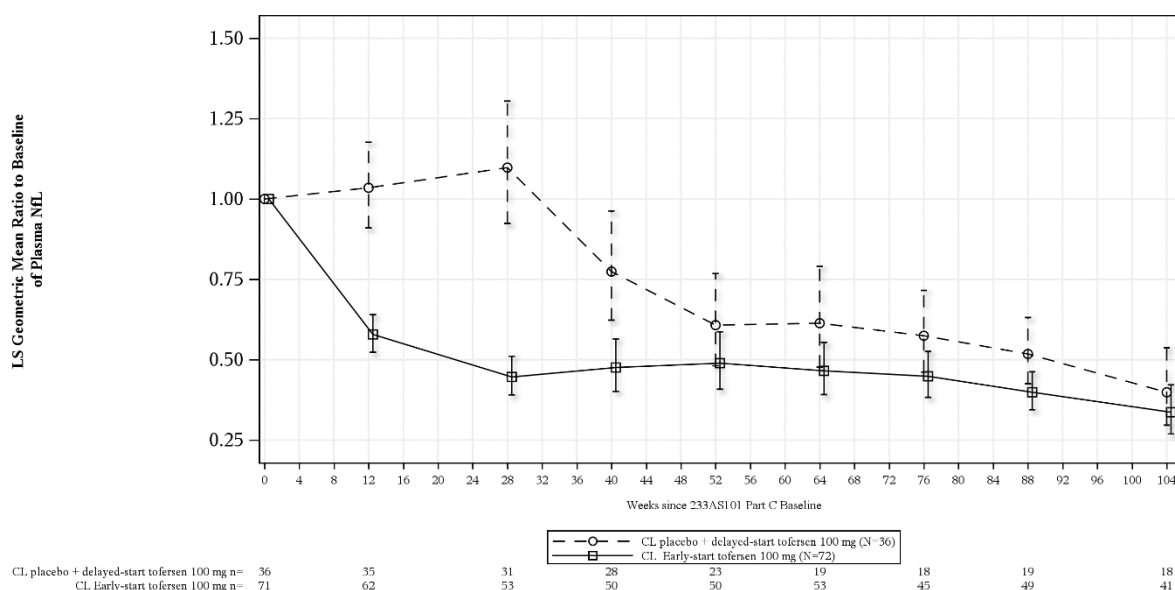
At Week 28 in Study 101 Part C, a reduction in total CSF SOD1 protein of 35% (geometric mean ratio to baseline) in the tofersen-treated group versus a 2% decrease from baseline in the corresponding placebo participants in the ITT population was observed (difference in geometric mean ratios for tofersen to placebo: 34% (95% CI: 23%, 43%). Total CSF SOD1 declined until approximately Day 56, after which the reductions were sustained over time.

### Plasma neurofilament light chain (NfL) biomarker

Plasma neurofilament light chain (NfL) was measured in Studies 101 Part C (VALOR) and 102 as a marker of axonal injury and neurodegeneration.

At Week 28 in Study 101 Part C, mean plasma NfL was reduced 55% (geometric mean ratio to baseline) in the tofersen-treated participants (ITT), compared to a 12% increase with placebo (difference in geometric mean ratios for tofersen to placebo: 60% (95% CI: 51%, 67%)). Plasma NfL levels declined until approximately Day 113, after which the reductions were sustained over time. The reductions in CSF NfL were consistent compared to those observed in plasma.

**Figure 1: Study 101 Part C: plasma NfL adjusted geometric mean ratio to baseline values by study week for the ITT population**



Abbreviations: NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.

Note 1: Baseline is defined as day 1 value prior to the clinical study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

Note 2: Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ, 4.9 pg/mL) in calculations. Multiple imputation is used for missing data.

Note 3: The ITT analysis is based on ANCOVA model with natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, baseline disease duration since symptom onset, and use of riluzole or edaravone.

Note 4: The table at the bottom presents the number of participants with observed non-missing data at each visit.

### Cardiac electrophysiology

ECG measurements and the values for the tofersen 100 mg group (n = 41) were similar to placebo group (n = 34) in Study 101 Part C. The incidence of abnormalities in ECG measurements was higher in the tofersen group compared to the placebo group, with 8 participants (11.3%) displaying a maximum increase from baseline in Fridericia formula (QTcF) > 30 to 60 ms in the tofersen group compared to 2 participants (5.6%) in the placebo group. The clinical significance of this imbalance is not known. No participants in the tofersen or placebo group displayed an increase from baseline in QTcF > 60 ms, and no participants displayed maximum postbaseline QTcF > 480 ms.

### Immunogenicity

Anti-drug antibodies (ADA) were very commonly detected. No evidence of ADA impact on efficacy or safety was observed. However, data are still limited.



## Clinical efficacy and safety

The efficacy of tofersen was assessed in a 28-week randomised, double-blind, placebo-controlled clinical study (Study 101, Part C) in participants aged 23 to 78 years with weakness attributable to ALS and a SOD1 mutation confirmed by central laboratory. One hundred eight (108) participants were randomised 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 participants who were on a stable dose for at least 30 or 60 days prior to study baseline, respectively.

Baseline disease characteristics in the overall intent to treat (ITT) population were generally similar in the tofersen-treated participants (n=72) and placebo participants (n=36), with a baseline ALS Functional Rating Scale–Revised (ALSFRS-R) total score of 36.9 (SD: 5.9) in the tofersen group and 37.3 (SD: 5.81) in the placebo group. The tofersen group had a shorter median time from symptom onset (11.4 months; range: 1.7, 145.7) as compared to the placebo group (14.6 months; range: 2.4, 103.2), and a higher median baseline plasma NfL level (78.5 pg/mL; range 5 to 329) as compared to the placebo group (64.6 pg/mL; range: 8 to 370).

The primary efficacy endpoint was the change from baseline to Week 28 in the ALSFRS-R total score. The results numerically favoured tofersen, but were not statistically significant (ITT population: tofersen-placebo adjusted mean difference [95% CI]: 1.4 [-1.3, 4.1]). Numerically larger differences were observed between tofersen and placebo over 28 weeks in patients with baseline NfL values above median [mean difference (95% CI) 3.9, (-1.0;8.9)] compared to patients with baseline NfL values below median [0.6, (-1.3,4.2)]. Secondary clinical outcomes also did not reach statistical significance.

## Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with tofersen in all subsets of the paediatric population in ALS (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under ‘exceptional circumstances’. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

## **5.2 Pharmacokinetic properties**

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

### 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; the accumulation ratio appears to be less than 2-fold. Tofersen is rapidly transferred from CSF into the systemic circulation, with a median time to maximum concentration ( $T_{max}$ ) plasma values ranged from 2 to 6 hours post intrathecal (IT) administration. There was no accumulation in plasma exposure measures ( $C_{max}$  and AUC) after monthly maintenance dosing.

### Distribution

Tofersen administered intrathecally was extensively distributed within the CNS, achieving therapeutic levels in the target spinal cord tissues. The median plasma AUC at 100 mg (Study 101 Part C data)

after first dose was 13973.1 ng/mL\*h; median maximum plasma concentration (C<sub>max</sub>) was 824.3 ng/mL, which occurred at between 4-6 hours post dose. The median plasma volume of distribution was estimated at 50.9L (119% CV) in study 101 and 102; and was 40.67 L (130% CV) in the 100 mg dose group. Pharmacokinetic (PK) analysis demonstrates that intrathecally administered tofersen is widely distributed into central nervous system (CNS) tissues and is rapidly transferred from CSF to the systemic circulation.

#### *Plasma Protein Binding*

Tofersen is highly bound to human plasma proteins ( $\geq 98\%$  bound) at clinically relevant or higher plasma concentrations (0.1 and 3  $\mu\text{g/ml}$ ), which limits glomerular filtration and reduces urinary excretion of the active substance. The likelihood of drug-drug interactions due to competition with plasma protein binding is very low.

#### Biotransformation

Tofersen is metabolised through exonuclease (3'- and 5')-mediated hydrolysis and is not a substrate for, or 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. The median plasma clearance was estimated at 8.32 L/hr (60.6% CV) in study 101 and 102; and was 5.73L/hr (60% CV) at 100 mg dose.

#### *Linearity/non-linearity*

In CSF, the pharmacokinetics of tofersen administered IT increase less than dose proportional for dose ranging from 20 mg to 100 mg.

In plasma, the pharmacokinetics of tofersen administered IT increase more than dose proportional for dose ranging from 20 mg to 100 mg.

#### *Immunogenicity*

The presence of anti-drug antibodies (ADAs) appeared to decrease plasma clearance by 28.0%.

#### Characteristics in specific patient populations

##### *Elderly*

Of the 166 patients who received tofersen in clinical studies, 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, but data are limited.

##### *Renal impairment*

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

##### *Hepatic impairment*

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

### **5.3 Preclinical safety data**

#### Carcinogenesis

Carcinogenicity studies with tofersen have not been performed.

## Mutagenesis

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).

## Reproductive toxicity

Reproductive toxicology studies were conducted using subcutaneous administration of tofersen in mice and rabbits. In a mice fertility and embryo-fetal development study, 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. 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. No tofersen-related adverse effects on embryo-foetal development were observed in mice and rabbits (at exposures more than 40-times the human exposure at MRHD). 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). Tofersen was detected in mouse milk samples from all tofersen-dosed animals. Tofersen is not pharmacologically active in mice and rabbits, which limits the validity of these studies, as harmful effects associated with SOD1 down-regulation cannot be evaluated therein.

Microscopic evaluation of reproductive tissues from both males and females in the 13-week and 39-week non-human primate (NHP) toxicology studies in which tofersen is pharmacologically active revealed no effects on the reproductive tissues.

## Toxicology

In a repeat-dose toxicology study (9 months), intrathecal 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 behaviour 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 human equivalent dose (HED) of 120 mg (based on the monkey-to-human CSF volume scaling). The safety margin (1.2-fold) for the IT doses in monkeys to IT doses in humans is based on the converted HED with consideration of volume difference in CSF (approximately 10-fold between human and monkeys). Therefore, no toxicity effects were seen at dose levels equivalent to 120 mg in humans.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Disodium phosphate  
Potassium chloride  
Calcium chloride dihydrate  
Magnesium chloride hexahydrate  
Sodium chloride  
Sodium dihydrogen phosphate dihydrate  
Water for injections

## **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **6.3 Shelf life**

42 months

### Temporary storage conditions

The vial of Qalsody in its original carton can be stored for up to 14 days at room temperature (store below 30°C).

Unopened vials of Qalsody can be removed from and returned to the refrigerator, if necessary. Unopened vials can be removed from the original carton for not more than 6 hours per day at room temperature for a maximum of 6 days.

## **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

For temporary storage conditions of unopened vials of the medicinal product, see section 6.3.

## **6.5 Nature and contents of container**

20 ml clear Type I glass vial with chlorobutyl rubber stopper and an aluminium overseal with flip-off plastic button.

Qalsody is available in a pack of 1 vial.

## **6.6 Special precautions for disposal and other handling**

Aseptic technique must be used when preparing and administering tofersen intrathecally. For single use only.

Vial preparation instructions:

- The refrigerated vial should be allowed to warm to room temperature (25°C) prior to administration without external heat source.
- The vial should not be shaken.
- Qalsody contains no preservatives. Once drawn into the syringe, the solution should be administered immediately (within 4 hours since removal from refrigeration) at room temperature; otherwise, it must be discarded.
- The solution should be visually inspected prior to removal of the solution from the vial. The solution should be essentially free of visible particles. Only clear and colourless to slightly yellow solution should be administered. If not, the vial must not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Biogen Netherlands B.V.  
Prins Mauritslaan 13  
1171 LP Badhoevedorp  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/23/1783/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 May 2024

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Biogen Netherlands B.V.  
Prins Mauritslaan 13  
1171 LP Badhoevedorp  
The Netherlands

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## **E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

<b>Description</b>	<b>Due Date</b>
To further investigate the long-term efficacy and safety of tofersen in the treatment of SOD1-ALS, the MAH shall submit the final results of the ongoing long term extension study (Study 233AS102).	by 30 September 2025

To further investigate if initiation of tofersen in presymptomatic SOD1-ALS patients can delay or even prevent emergence of clinically manifested ALS (CMALS), the MAH shall submit the final results of the phase 3 study in patients with clinically presymptomatic SOD1-ALS (Study ATLAS 233AS303).	by 31 December 2028
To further characterise variant-specific survival, the MAH will provide the final results of the descriptive integrated analyses of disease duration (survival) by <i>SOD1</i> variant-type in tofersen-treated (Studies 101/102; disease registries) vs. patients untreated with tofersen (disease registries, natural history datasets/literature).	by 30 June 2027
To further evaluate the long-term safety of tofersen in patients with SOD1-ALS, the MAH shall conduct and submit the results of an observational registry-based study 233AS401 according to the agreed protocol.	Annually (with annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of tofersen in the treatment of patients with SOD1-ALS, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of tofersen.	Annually (with annual reassessment)



**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Qalsody 100 mg solution for injection  
tofersen

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each 15 ml vial contains 100 mg tofersen (6.7 mg/ml).

**3. LIST OF EXCIPIENTS**

Disodium phosphate, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intrathecal use.  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original package in order to protect from light.

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
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<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
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Biogen Netherlands B.V.  
Prins Mauritslaan 13  
1171 LP Badhoevedorp  
The Netherlands

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/23/1783/001

<b>13. BATCH NUMBER</b>
-------------------------

Lot

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
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<b>15. INSTRUCTIONS ON USE</b>
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<b>16. INFORMATION IN BRAILLE</b>
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Justification for not including Braille accepted.

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
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2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS****VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Qalsody 100 mg solution for injection  
tofersen  
intrathecal use

**2. METHOD OF ADMINISTRATION****3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

100 mg/15 ml

**6. OTHER**

## **B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### **Qalsody 100 mg solution for injection** tofersen

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Qalsody is and what it is used for
2. What you need to know before you are given Qalsody
3. How Qalsody is given
4. Possible side effects
5. How to store Qalsody
6. Contents of the pack and other information

#### **1. What Qalsody is and what it is used for**

Qalsody contains the active substance tofersen which belongs to a group of medicines known as *antisense oligonucleotides*.

This medicine is used in adults to treat a type of *amyotrophic lateral sclerosis* (ALS) caused by mutations (changes) in a gene called SOD1.

ALS caused by mutations in the *SOD1* gene is a rare type of motor neuron disease that affects the nerve cells in the brain and spinal cord. Mutations in the SOD1 gene cause a build-up of a toxic form of the SOD1 protein. This causes destruction of motor neurons (the nerve cells responsible for sending instructions to the muscle), leading to weakness and wasting in the muscles, including those used for breathing and swallowing.

Qalsody works by reducing the build-up of SOD1 protein. This helps to prevent the destruction of motor neurons and may slow the loss of muscle strength.

#### **2. What you need to know before you are given Qalsody**

##### **Qalsody must not be given**

- if you are **allergic to tofersen** or any of the other ingredients of this medicine (listed in section 6).

**Talk to your doctor or nurse** before you start treatment if this applies to you.

#### **Warnings and precautions**

There is a risk of side effects occurring after Qalsody is given by lumbar puncture procedure (see section 3). This can include headaches, back pain and infection.

There have been a small number of reports of patients developing inflammation of the spinal cord (*myelitis*) or irritation or injury to the nerve roots (*radiculitis*) after Qalsody is given. You need to know about the symptoms of this while you are on this medicine. See *Serious side effects* in section 4 of this leaflet.

There have been a small number of reports of patients developing swelling of the optic nerve in the eye (*papilloedema*) and/or an increase in the pressure around the brain (increased intracranial pressure) in patients treated with Qalsody. See *Serious side effects* in section 4 of this leaflet.

### **Tests before treatment**

You may have a **urine test** (to check your kidneys) and a **blood test** (to check that your blood clots properly) before you start treatment. This is because other medicines in the same group as Qalsody can affect the kidneys and the cells in the blood which help clotting. These tests may not be needed every time you are given Qalsody.

### **Children and adolescents**

This medicine should not be given to children and adolescents under 18 years of age. The use of this medicine in patients under age of 18 has not been studied.

### **Other medicines and Qalsody**

Tell your doctor if you are taking, have recently taken or might take any other medicines.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

#### **Pregnancy**

Qalsody is not recommended to be used during pregnancy and in women of childbearing potential not using contraception.

#### **Breast-feeding**

Your doctor will help you to decide whether you should continue breast-feeding or to start treatment with Qalsody. Your doctor will consider the possible benefits of treatment for you compared with the benefits of breast-feeding for your baby.

### **Driving and using machines**

This medicine may affect your ability to drive or use machines.

Do not drive or use machines if you notice a change in your vision with Qalsody.

### **Qalsody contains sodium**

This medicine contains 52 mg sodium (main component of cooking/table salt) in each 15 ml. This is equivalent to 3% of the recommended maximum daily dietary intake of sodium for an adult.

### **Qalsody contains potassium**

This medicine contains less than 1 mmol (39 mg) potassium per 15 ml dose, i.e. essentially 'potassium-free'.

## **3. How Qalsody is given**

The recommended dose is 100 mg tofersen. The first three doses will be given at 14-day intervals on day 1, day 15 and day 29 of treatment. Qalsody will then be given every 28 days.



This medicine is given by intrathecal (into the fluid surrounding the spinal cord) injection into the lower back by a lumbar puncture. This is done by inserting a needle into the space around the spinal cord. This will be done by a doctor experienced in doing lumbar punctures.

#### **How long Qalsody is used for**

Your doctor will discuss with you how long you will need to receive Qalsody. Do not stop treatment with Qalsody without talking to your doctor.

#### **If you miss a Qalsody injection**

If you miss a dose of Qalsody, speak to your doctor so that it can be given as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects related to the lumbar puncture may occur while Qalsody is being given or afterwards. The side effects can include headache, back pain and infection.

#### **Serious side effects**

The most serious side effects seen in patients receiving Qalsody have been inflammation of the spinal cord (*myelitis*) or irritation and injury of nerve roots (*radiculitis*). Common symptoms may include:

- weakness
- numbness
- abnormal sensations (pins and needles)
- pain.

Swelling of the nerve that connects the eyes with the brain (*papilloedema*) and increased pressure around your brain (increased intracranial pressure) have also been reported. Papilloedema can result from increased intracranial pressure. Common symptoms may include:

- blurred vision
- double vision
- vision loss
- headache.

Inflammation of the lining around the brain and spinal cord (*aseptic or chemical meningitis*) has been reported. This is not caused by an infection. Common symptoms may include:

- headache
- fever
- neck stiffness
- nausea
- vomiting.

**Tell your doctor immediately**, if you have any of the symptoms listed above.

#### **Other side effects**

**Very common** (*may affect more than 1 in 10 people*)

- pain (back pain, pain in arms or legs)
- feeling tired
- muscle and joint pain
- fever
- increase in protein and/or white blood cell count occurring in the fluid that surrounds the brain and spinal cord.

**Common** (*may affect up to 1 in 10 people*)

- muscle stiffness
- nerve pain, including burning, stabbing, pins and needles sensations.

**Tell your doctor** if you notice these or any new symptoms that concern you.

### **Reporting of side effects**

If you get any side effects, talk to your **doctor, pharmacist** or **nurse**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Qalsody**

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

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice particles in the solution or if the liquid in the vial is not clear and colourless.

**Store in a refrigerator** (2°C - 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

The vial of Qalsody in its original carton can be stored for up to 14 days at room temperature (store below 30°C).

Unopened vials of Qalsody can be removed from and returned to the refrigerator, if necessary.

Unopened vials can be removed from the original carton for not more than 6 hours per day at room temperature for a maximum of 6 days.

## **6. Contents of the pack and other information**

### **What Qalsody contains**

- The active substance is tofersen
- Each 15 ml vial contains 100 mg of tofersen.
- Each ml contains 6.7 mg of tofersen.
- The other ingredients are disodium phosphate, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections.

### **What Qalsody looks like and contents of the pack**

Qalsody is a clear, colourless to slightly yellow solution for injection.

Each carton of Qalsody contains one vial.

### **Marketing Authorisation Holder and Manufacturer**

Biogen Netherlands B.V.

Prins Mauritslaan 13

1171 LP Badhoevedorp

The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

**This leaflet was last revised in.**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<https://www.ema.europa.eu>.