

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

Spinraza 12 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml vial contains nusinersen sodium equivalent to 12 mg nusinersen.
Each ml contains 2.4 mg of nusinersen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution with pH of approximately 7.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy.

4.2 Posology and method of administration

Treatment with Spinraza should only be initiated by a physician with experience in the management of spinal muscular atrophy (SMA).

The decision to treat should be based on an individualised expert evaluation of the expected benefits of treatment for that individual, balanced against the potential risk of treatment with Spinraza. Patients with profound hypotonia and respiratory failure at birth, where Spinraza has not been studied, may not experience a clinically meaningful benefit due to severe SMN protein deficiency.

Posology

The recommended dosage is 12 mg (5 ml) per administration.

Spinraza treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter.

Duration of treatment

Information on long term efficacy of this medicinal product is not available. 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.

Missed or delayed doses

If a loading dose is delayed or missed Spinraza should be administered as soon as possible, with at least 14 days between doses, and continue dosing at the prescribed frequency. If a maintenance dose is delayed or missed, Spinraza should be administered as soon as possible and dosing continued every 4 months.

Special populations

Renal impairment

Spinraza has not been studied in patients with renal impairment. The safety and efficacy in patients with renal impairment has not been established and they should be closely observed.

Hepatic impairment

Spinraza has not been studied in patients with hepatic impairment. Spinraza is not metabolised via the cytochrome P450 enzyme system in the liver, therefore dose adjustment is unlikely to be required in patients with hepatic impairment (see sections 4.5 and 5.2).

Method of administration

Spinraza is for intrathecal use by lumbar puncture.

Treatment should be administered by health care professionals experienced in performing lumbar punctures.

Spinraza is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anaesthesia needle. The injection must not be administered in areas of the skin where there are signs of infection or inflammation. It is recommended that the volume of cerebral spinal fluid (CSF), equivalent to the volume of Spinraza to be injected, is removed prior to administration of Spinraza.

Sedation may be required to administer Spinraza, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of Spinraza, particularly in younger patients and in patients with scoliosis. Aseptic technique should be used when preparing and administering Spinraza; see instructions for use in section 6.6.

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, vomiting; see section 4.8). Potential difficulties with this route of administration may be seen in very young patients and those with scoliosis. The use of ultrasound or other imaging techniques to assist with intrathecal administration of Spinraza, can be considered at the physician's discretion.

Thrombocytopenia and coagulation abnormalities

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

Renal toxicity

Renal toxicity has been observed after administration of other 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. *In vitro* studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism. *In vitro* studies indicate that the likelihood for interactions with nusinersen due to competition for plasma protein binding, or competition with or inhibition of transporters is low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of nusinersen in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Spinraza during pregnancy.

Breast-feeding

It is unknown whether nusinersen/metabolites are excreted in human milk.

A risk to the newborn/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Spinraza therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In toxicity studies in animals no effects on male or female fertility were observed (see section 5.3). There are no data available on the potential effects on fertility in humans.

4.7 Effects on ability to drive and use machines

Spinraza has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The safety assessment of Spinraza was based on two Phase 3 clinical studies in infants (CS3B) and children (CS4) with SMA, together with open-label studies including pre-symptomatic infants genetically diagnosed with SMA and infants and children with SMA. Of the 260 patients who received Spinraza up to a maximum of 4 years, 154 patients received treatment for at least 1 year.

Tabulated list of adverse reactions

The assessment of undesirable effects is based on the following frequency data:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Table 1: Adverse reactions related to lumbar puncture procedure reported in CS4 (later onset SMA) with an incidence at least 5% higher in patients treated with Spinraza than sham-control

MedDRA System Organ Class	MedDRA preferred term	Spinraza frequency category, n=84
Nervous system disorders	Headache [*]	Very common
Gastrointestinal disorders	Vomiting [*]	common
Musculoskeletal and connective tissue disorders	Back pain [*]	Very common

^{*}Adverse events considered related to the lumbar puncture procedure. These events can be considered manifestations of post-lumbar puncture syndrome.

Description of selected adverse reactions

Adverse reactions associated with the administration of Spinraza by lumbar puncture have been observed. The majority of these are reported within 72 hours of the procedure. The incidence and severity of these events were consistent with events expected to occur with lumbar puncture. No serious complications of lumbar puncture, such as serious infections, have been observed in the clinical trials of Spinraza.

Some adverse events commonly associated with lumbar puncture (e.g. headache and back pain) could not be assessed in the infant population exposed to Spinraza due to the limited communication appropriate for that age group.

Immunogenicity

The immunogenic response to nusinersen was determined in 148 patients with baseline and post-baseline plasma samples evaluated for anti-drug antibodies (ADA). Overall, the incidence of ADAs was low, with 7 (5%) patients developing treatment-emergent ADAs, of which 2 were transient and 2 were considered to be persistent, and 3 were unconfirmed. There was no apparent effect of ADA development on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

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 adverse reactions 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: {group}, ATC code: **not yet assigned**

Mechanism of action

Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts by binding to an

intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein.

SMA is a progressive neuromuscular disease resulting from mutations in chromosome 5q in the SMN1 gene. A second gene SMN2, located near SMN1, is responsible for a small amount of SMN protein production. SMA is a clinical spectrum of disease with disease severity linked to fewer numbers of SMN2 gene copies and younger age of symptom onset.

Clinical efficacy and safety

Symptomatic patients

Infantile onset

Study CS3B (ENDEAR) was a Phase 3, randomized, double-blind, sham-procedure controlled study conducted in 121 symptomatic infants ≤ 7 months of age, diagnosed with SMA (symptom onset before 6 months of age). CS3B was designed to assess the effect of Spinraza on motor function and survival. Patients were randomized 2:1 to either Spinraza (as per the approved dosing regimen) or sham-control, with a length of treatment ranging from 6 to 442 days.

The median age of onset of clinical signs and symptoms of SMA was 6.5 weeks and 8 weeks for Spinraza treated versus sham-control patients respectively, with 99% of patients having 2 copies of the SMN2 gene and therefore deemed most likely to develop Type I SMA. The median age when patients received their first dose was 164.5 days for treated patients, and 205 days for sham-control. Baseline disease characteristics were largely similar in the Spinraza treated patients and sham-control patients except that Spinraza treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

At the final analysis, a statistically significant greater percentage of patients achieved the definition of a motor milestone responder in the Spinraza group (51%) compared to the sham-control group (0%) ($p < 0.0001$). Time to death or permanent ventilation (≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy) was assessed as the primary endpoint. Statistically significant effects on event-free survival, overall survival, the proportion of patients achieving the definition of a motor milestone responder, and the percentage of patients with at least a 4-point improvement from baseline in Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) score were observed in patients in the Spinraza group compared to those in the sham-control group (Table 2).

In the efficacy set, 18 patients (25%) in the Spinraza group and 12 patients (32%) in the sham-control group required permanent ventilation. Of these patients, 6 (33%) in the Spinraza group and 0 (0%) in the sham-control group met the protocol-defined criteria for a motor-milestone responder.

Table 2: Primary and secondary endpoints at final analysis – Study CS3B

Efficacy Parameter	Spinraza treated Patients	Sham-control Patients
Survival		
Event-free survival²		
Number of patients who died or received permanent ventilation	31 (39%)	28 (68%)
Hazard ratio (95% CI)	0.53 (0.32 -0.89)	
p-value	p = 0.0046	
Overall survival²		
Number of patients who died	13 (16%)	16 (39%)

Efficacy Parameter	Spinraza treated Patients	Sham-control Patients
Hazard Ratio (95% CI) p-value	0.37 (0.18 – 0.77) p=0.0041	
Motor function		
Motor milestones³		
Proportion achieving pre-defined motor milestone responder criteria (HINE section 2) ^{4,5}	37 (51%) ¹ p<0.0001	0 (0%)
Proportion at Day 183	41%	5%
Proportion at Day 302	45%	0%
Proportion at Day 394	54%	0%
Proportion with improvement in total motor milestone score	49 (67%)	5 (14%)
Proportion with worsening in total motor milestone score	1 (1%)	8 (22%)
CHOP INTEND³		
Proportion achieving a 4-point improvement	52 (71%) p<0.0001	1 (3%)
Proportion achieving a 4-point worsening	2 (3%)	17 (46%)
Proportion with any improvement	53 (73%)	1 (3%)
Proportion with any worsening	5 (7%)	18 (49%)

¹CS3B was stopped following positive statistical analysis on the primary endpoint at interim analysis (statistically significantly greater percentage of patients achieved the definition of a motor milestone responder in the Spinraza group (41%) compared to the sham-control group (0%), p<0.0001)

²At the final analysis, event-free survival and overall survival were assessed using the Intent to Treat population (ITT Spinraza n=80; Sham-control n=41).

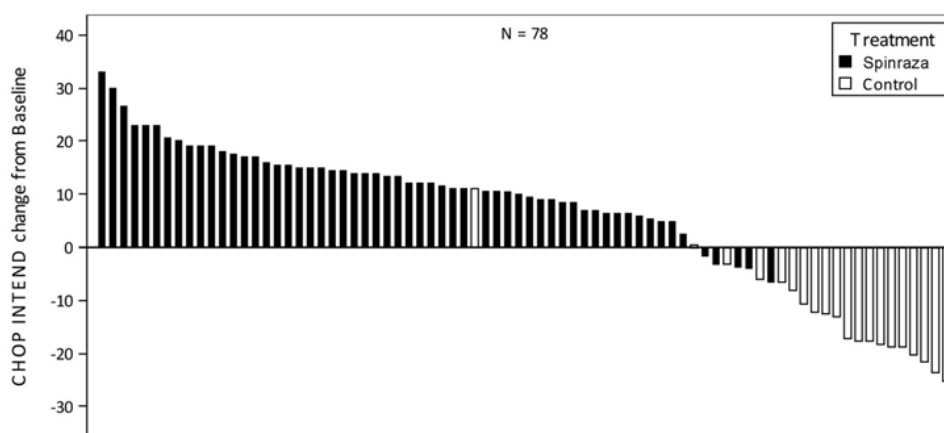
³At the final analysis, CHOP INTEND and motor milestone analyses were conducted using the Efficacy Set (Spinraza n=73; Sham-control n=37).

⁴Assessed at the later of Day 183, Day 302, and Day 394 Study Visit

⁵According to Hammersmith Infant Neurological Examination (HINE) section 2: ≥ 2 point increase [or maximal score] in ability to kick, OR ≥ 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening, defined as a responder for this primary analysis.

The extent of improvement in CHOP INTEND is shown in Figure 1(change from baseline score for each subject).

Figure 1: Change in CHOP INTEND from Baseline to Later of Day 183, Day 302, and Day 394 Study Visit – Endear Study /CS3B (Efficacy Set, ES)



Note 1: Shortest bars at 0 line indicate 0 value.

Note 2: Out of the 110 patients in the efficacy set, 29 died (13 (18%) for Spinraza and 16 (43%) for Control) and 3 withdrew for reason other than death (2 (3%) for Spinraza and 1 (3%) for Control) and were therefore not included in this analysis of the ES.

These results are supported by an open-label Phase 2 study in symptomatic patients diagnosed with SMA (CS3A). Median age of onset of clinical signs and symptoms was 56 days and patients had either 2 SMN2 gene copies (n=17) or 3 SMN2 gene copies (n=2) (SMN2 gene copy number unknown for 1 patient). Patients in this study were deemed most likely to develop Type I SMA. The median age at first dose was 162 days.

At the time of the planned interim analysis patients in the study had a median time on study of 670 days. The primary endpoint was the proportion of patients who improved in one or more categories in motor milestones (according to HINE section 2: ≥ 2 point increase [or maximal score] in ability to kick or voluntary grasp OR ≥ 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking). At this time, 13 out of 20 patients (65%) had met the primary endpoint with a sustained improvement in mean motor milestone achievement over time. A sustained improvement in mean CHOP INTEND score was observed from baseline to day 694 (mean change 16.90). Overall, 11 out of 20 patients (55%) met the endpoint of an increase in total CHOP INTEND score of ≥ 4 points as of their last study visit prior to data cut-off.

Later onset

Study CS4 (CHERISH) is a Phase 3, randomised, double-blind, sham-procedure controlled study conducted in 126 symptomatic patients with later-onset SMA (symptom onset after 6 months of age). Patients were randomized 2:1 to either Spinraza (dosed with 3 loading doses and maintenance doses every 6 months) or sham-control, with a length of treatment ranging from 170 to 470 days. The median age at screening was 3 years, and the median age of onset of clinical signs and symptoms of SMA was 11 months. The majority of patients (88%) have 3 copies of the SMN2 gene (8% have 2 copies, 2% have 4 copies, and 2% have an unknown copy number). Patients in this study were deemed most likely to develop Type II or III SMA. Baseline disease characteristics were generally similar with the exception of an imbalance in the proportion of patients who had ever achieved the ability to stand without support (13% of patients in the Spinraza group and 29% in sham-control) or walk with support (24% of patients in the Spinraza group and 33% in sham-control).

An interim analysis was conducted when all patients had completed their month 6 assessment and at least 39 patients had completed their Month 15 assessment, see Table 3. The primary endpoint assessed at the time of interim analysis was change from baseline score at Month 15 on the Hammersmith Functional Motor Scale Expanded (HFMSE). The primary analysis was conducted in the ITT population (Spinraza: n=84; sham-control: n=42), and post-baseline HFMSE data for patients without a Month 15 visit were imputed using the multiple imputation method. A statistically significant improvement from baseline HFMSE score was observed in Spinraza treated patients compared to the sham-control patients. An analysis of the subset of patients in the ITT population who had observed values at Month 15 demonstrated consistent, statistically significant results. Descriptive results from additional functional measures including revised upper limb module test and WHO motor milestone achievement are described in Table 3.

Initiation of treatment sooner after symptom onset resulted in earlier and greater improvement in motor function than those with delayed treatment initiation; however, both groups experienced benefit compared to sham-control.

Table 3: Primary and secondary endpoints at interim analysis – Study CS4¹

	Spinraza treated Patients	Sham-control Patients
HFMSE score Change from baseline in total HFMSE score at 15 months ^{1,2}	4.0 (95% CI: 2.9, 5.1) p=0.0000002	-1.9 (95% CI: -3.8, 0.0)
Proportion of patients who achieved at least a 3 point improvement from baseline ^{1,3}	57.3%	20.5%
RULM⁵ Mean change from baseline to month 15 in total RULM score ^{1,2,3}	3.7	0.3
WHO motor milestones Proportion of patients who achieved any new motor milestone at 15 months ^{3,4}	17.1	10.5

¹CS4 was stopped following positive statistical analysis on the primary endpoint

²Least squares mean

³Not statistically tested at the interim analysis

⁴WHO milestone achievement was assessed using the Interim Efficacy Set population (IES, Spinraza n=35; Sham-control n=19); analyses are based on imputed data when there are missing data.

⁵RULM (Revised upper limb module)

These results are supported by 2 open label studies (study CS2 and study CS12). The analysis included 28 patients who received their first dose in study CS2, and then transferred to the extension phase, study CS12. The studies enrolled patients who were between 2 to 15 years of age at first dose. Of the 28 patients, 3 were at least 18 years of age at their last study visit. 1 out of 28 patients had 2 SMN2 gene copies, 21 had 3 copies, and 6 had 4 copies.

Patients were assessed over a 3 year treatment period. A sustained improvement was seen in patients with Type II, with a mean improvement from baseline HFSME score of 12.3 (SD 5.46, n=6), with a mean total score of 35.3 (SD 12.58) after 1050 days of treatment, no plateau was observed. Patients with Type III SMA demonstrated a mean improvement from baseline HFSME score of 1.6 (SD 3.91, n=7), with a mean total score of 53.0 (SD 9.22) after 1050 days.

The 6MWT (six-minute walk test) was conducted for ambulatory patients only. In these patients, a mean improvement of 96.7 metres (SD 42.36, n=6), with a mean 6MWT distance of 278.2 metres (SD 157.58) was observed after 1050 days. Two previously non-independent ambulatory patients (Type III) achieved independent walking, and one non-ambulatory patient (Type II) achieved independent walking.

Pre-symptomatic infants

Study CS5 (NURTURE) is an open-label study in pre-symptomatic infants genetically diagnosed with SMA, who were enrolled at 6 weeks of age or younger. Patients in this study were deemed most likely to develop Type I or II SMA. Median age at first dose was 19 days.

At the interim analysis, 18 of the 20 patients completed the Day 64 visit, thereby composing the Efficacy Set (2 SMN2 gene copies, n=13; 3 SMN2 gene copies, n=5). The median time on study was 317.5 days. The primary endpoint assessed at the time of the interim analysis was time to death or respiratory intervention (defined as invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 consecutive days OR tracheostomy). At the planned interim analysis, no patients had met the primary endpoint of death or respiratory intervention.

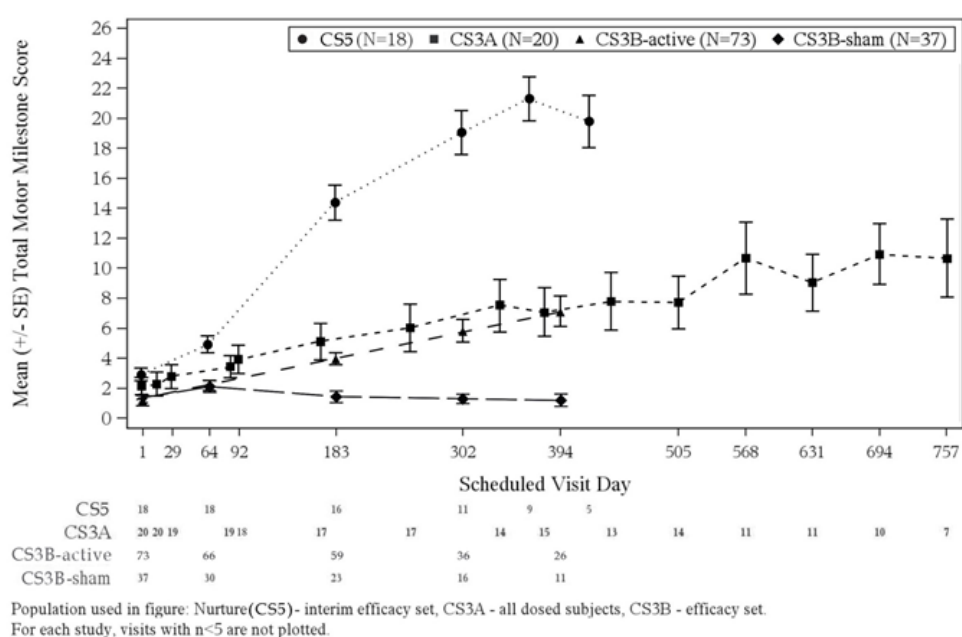
Patients achieved milestones unexpected in Type I or II SMA and more consistent with normal development. Compared to baseline, improvements in HINE motor milestones were achieved in

16 patients (89%) in the efficacy set at the interim analysis. Twelve patients were sitting independently, 9 were standing with or without support, and 6 were walking with or without support. Sixteen patients (89%) demonstrated a ≥ 4 -point improvement in CHOP INTEND total score, 7 of which achieved the maximum total CHOP INTEND score of 64. One subject (6%) experienced a ≥ 4 -point decrease in CHOP INTEND total score.

The proportion of patients developing clinically manifested SMA was assessed amongst patients who reached the Day 365 visit at the interim analysis (n=9). The protocol-defined criteria for clinically manifested SMA included age-adjusted weight below the fifth WHO percentile, a decrease of 2 or more major weight growth curve percentiles, the placement of a percutaneous gastric tube, and/or the inability to achieve expected age-appropriate WHO milestones (independent sitting, standing with assistance, and hands-and-knees crawling). Five (56%) patients were gaining weight and achieving WHO milestones consistent with normal development. Although 4 patients (44%) (each with 2 SMN2 gene copies) met the protocol-defined criteria, these patients were gaining weight and achieving WHO milestones, including independent sitting, inconsistent with Type I SMA.

A comparison of motor milestone achievement among the patients with symptomatic infantile-onset SMA and pre-symptomatic SMA is shown in Figure 2.

Figure 2: Change in HINE Motor Milestones versus Study days for Study CS3B (treated and sham-control), CS3A and CS5



5.2 Pharmacokinetic properties

Single- and multiple-dose pharmacokinetics (PK) of nusinersen, administered via intrathecal injection, were determined in paediatric patients diagnosed with SMA.

Absorption

Intrathecal injection of nusinersen into the CSF allows nusinersen to be fully available for distribution from the CSF to the target central nervous system (CNS) tissues. Mean CSF trough concentrations of nusinersen accumulated approximately 1.4- to 3-fold after multiple loading and maintenance doses, and reached a steady state within approximately 24 months. Following intrathecal administration trough plasma concentrations of nusinersen were relatively low compared to the trough CSF concentration. Median plasma T_{max} values ranged from 1.7 to 6.0 hours. Mean plasma C_{max} and AUC values increased approximately dose proportionally over the evaluated dose range. There is no accumulation in plasma exposure measures (C_{max} and AUC) after multiple doses.

Distribution

Autopsy data from patients (n=3) show that nusinersen administered intrathecally is broadly distributed within the CNS achieving therapeutic levels in the target spinal cord tissues. Presence of nusinersen was also demonstrated in neurons and other cell types in the spinal cord and brain, and peripheral tissues such as skeletal muscle, liver, and kidney.

Biotransformation

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

Elimination

The mean terminal elimination half-life in CSF is estimated at 135 to 177 days. The primary route of elimination is expected via urinary excretion of nusinersen and its metabolites.

Interactions

In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450-mediated oxidative metabolism and therefore should not interfere with other medicinal products for these metabolic pathways. Nusinersen is not a substrate or inhibitor of human BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or BSEP transporters.

Characteristics in specific patient populations

Renal and hepatic impairment

The pharmacokinetics of nusinersen in patients with renal or hepatic impairment has not been studied. The effect of hepatic or renal insufficiency as covariates could not be thoroughly evaluated in the population PK model given the rarity of patients displaying clinically relevant liver or kidney insufficiencies. Population PK analyses revealed no apparent correlation between hepatic and renal clinical chemistry markers and inter-subject variability.

Race

The majority of patients studied were Caucasian. The population PK analysis suggests that race is unlikely to affect the PK of nusinersen.

5.3 Preclinical safety data

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of nusinersen have not been performed.

Mutagenesis

Nusinersen demonstrated no evidence of genotoxicity.

Reproductive toxicity

Reproductive toxicology studies were conducted using subcutaneous administration of nusinersen in mice and rabbits. No impact on male or female fertility, or embryo-foetal development, or pre/post-natal development was observed.

Toxicology

In repeat-dose toxicity studies (14-weeks and 53-weeks) of intrathecal administration to juvenile cynomolgus monkeys, nusinersen was well tolerated. The exception was an acute, transient deficit in lower spinal reflexes which occurred at the highest dose levels in each study (3 or 4 mg per dose; equivalent to 30 or 40 mg per intrathecal dose in patients). These effects were observed within several hours post-dose and generally resolved within 48 hours.

In the 53-week intrathecal dosing study in cynomolgus monkeys no toxicity effects were seen at levels up to 14-fold the recommended annual clinical maintenance dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium phosphate
Sodium chloride
Potassium chloride
Calcium chloride dihydrate
Magnesium chloride hexahydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

If no refrigeration is available, Spinraza may be stored in its original carton, protected from light at or below 30°C for up to 14 days.

Prior to administration, unopened vials of Spinraza can be removed from and returned to the refrigerator if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours, at a temperature that does not exceed 25°C.

6.5 Nature and contents of container

5 ml in a Type I glass vial with bromobutyl rubber stopper and an aluminium over-seal and plastic cap.

Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

For single use only.

Instructions for preparation of the medicinal product before administration

1. The Spinraza vial should be inspected for particles prior to administration. If particles are observed and/or the liquid in the vial is not clear and colourless, the vial must not be used.
2. Aseptic technique should be used when preparing Spinraza solution for intrathecal administration.
3. The vial should be taken out of the refrigerator and allowed to warm to room temperature (25°C) without using external heat sources, prior to administration.
4. If the vial remains unopened and the solution is not used, it should be returned back to the refrigerator (see section 6.4).
5. Just prior to administration, remove the plastic cap and insert the syringe needle into the vial through the centre of the over-seal to remove the appropriate volume. Spinraza must not be diluted. The use of external filters is not required.
6. Once drawn in to the syringe, if the solution is not used within 6 hours, it must be discarded.
7. Any unused product or waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1188/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://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**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Biogen (Denmark) Manufacturing ApS
Biogen Allé 1
DK - 3400 Hillerød
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to 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

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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.

• Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to evaluate the long term efficacy and safety of nusinersen in symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 3, open-label extension study (SHINE, CS11)	Submission of study results: August 2023.

Post-authorisation efficacy study (PAES): In order to evaluate the long term efficacy and safety of nusinersen in pre-symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 2, open-label study (NURTURE (SM201))	Submission of study results: April 2023.
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ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

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

Spinraza 12 mg solution for injection
nusinersen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5 ml vial contains nusinersen sodium equivalent to 12 mg nusinersen (2.4 mg/ml).

3. LIST OF EXCIPIENTS

Sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium hydroxide, hydrochloric acid, 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 carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Biogen Idec Ltd
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1188/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

Spinraza 12 mg solution for injection
nusinersen
Intrathecal use

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

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Spinraza 12 mg solution for injection

nusinersen

▼ 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 or your child receives 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 or nurse.
- If you or your child gets any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Spinraza is and what it is used for

Spinraza contains the active substance *nusinersen* which belongs to a group of medicines known as *antisense oligonucleotides*. Spinraza is used to treat a genetic disease called *spinal muscular atrophy* (SMA).

Spinal muscular atrophy is caused by a shortage of a protein called *survival motor neuron* (SMN) in the body. This results in the loss of nerve cells in the spine, leading to weakness of the muscles in the shoulders, hips, thighs and upper back. It may also weaken the muscles used for breathing and swallowing.

Spinraza works by helping the body to produce more of the SMN protein that people with SMA are lacking. This reduces the loss of nerve cells and so may improve muscle strength.

2. What you need to know before you or your child are given Spinraza

Spinraza must not be given:

- If you or your child are **allergic to nusinersen** or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before you or your child are given Spinraza.

Warnings and precautions

There is a risk of side effects occurring after Spinraza is given by a lumbar puncture procedure (see section 3). This can include headaches, vomiting and back pain. There may also be difficulties with giving a medicine by this method in very young patients and those with scoliosis (twisted and curved spine).

Other products that are in the same group of medicines as Spinraza have been shown to affect the cells in the blood which help clotting. Before you or your child are given Spinraza your doctor may decide to do a blood test to check that your or your child's blood can clot properly. This may not be required every time you or your child are given Spinraza.

Other products that are in the same group of medicines as Spinraza have been shown to affect the kidneys. Before you or your child are given Spinraza your doctor may decide to do a urine test to check that your or your child's kidneys are working normally. This may not be required every time you or your child are given Spinraza.

Talk to your doctor before you or your child are given Spinraza.

Other medicines and Spinraza

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

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 being given this medicine. It is preferable to avoid the use of Spinraza during pregnancy and breast-feeding.

Driving and using machines

Spinraza has no or negligible influence on the ability to drive and use machines.

Spinraza contains a small amount of sodium

Each dose of Spinraza contains less than 1 mmol (23 mg) sodium. It is essentially 'sodium-free' and can be used by people on a sodium-restricted diet.

3. How Spinraza is given

The usual dose of Spinraza is 12 mg.

Spinraza is given;

- On the first day of treatment, day 0
- Then around day 14, day 28 and day 63
- Then once every 4 months.

Spinraza is given by injection into the lower back. This injection, called a lumbar puncture, 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. You or your child may also be given a medicine to make you relax or sleep during the procedure.

How long to use Spinraza

Your doctor will tell you how long you or your child need to receive Spinraza. Don't stop treatment with Spinraza unless your doctor tells you to.

If you or your child misses an injection

If you or your child miss a dose of Spinraza, speak with your doctor so that Spinraza can be given as soon as possible.

If you have any questions about how Spinraza is given, ask your doctor.

4. Possible side effects

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

Side effects of the lumbar puncture

Side effects related to the lumbar puncture may occur while Spinraza is being given or shortly afterwards. The majority of these side effects are reported within 72 hours of the procedure.

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

- Back pain
- Headache

Common side effects (may affect up to 1 in 10 people)

- Vomiting.

Reporting of side effects

If you or your child get any side effects, talk to your doctor 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 Spinraza

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.

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

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

If no refrigeration is available, Spinraza may be stored in its original carton, protected from light at or below 30°C for up to 14 days.

Unopened vials of Spinraza can be removed from and returned to the refrigerator if necessary. If removed from the original carton, the total time out of refrigeration should not exceed 30 hours, at a temperature that does not exceed 25°C.

6. Contents of the pack and other information

What Spinraza contains

- The active substance is nusinersen.
- Each 5 ml vial contains nusinersen sodium equivalent to 12 mg nusinersen.
- Each ml contains 2.4 mg of nusinersen.
- The other ingredients are sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium hydroxide, hydrochloric acid, water for injections.

What Spinraza looks like and contents of the pack

Spinraza is a clear colourless solution for injection.

Each carton of Spinraza contains one vial.

Each vial is for single use.

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Manufacturer

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This leaflet was last revised in

Other sources of information

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

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The following information is intended for healthcare professionals only:

1. The Spinraza vial should be inspected for particles prior to administration. If particles are observed and/or the liquid in the vial is not clear and colourless, the vial must not be used.
2. Aseptic technique should be used when preparing Spinraza solution for intrathecal administration.
3. The vial should be taken out of the refrigerator and allowed to warm to room temperature (25°C) without using external heat sources, prior to administration.
4. If the vial remains unopened and the solution is not used, it should be returned back to the refrigerator.
5. Just prior to administration, remove the plastic cap and insert the syringe needle into the vial through the center of the over-seal to remove the appropriate volume. Spinraza must not be diluted. The use of external filters is not required.
6. Spinraza is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anaesthesia needle.
7. The injection must not be administered in areas of the skin where there are signs of infection or inflammation.

8. It is recommended that the volume of CSF, equivalent to the volume of Spinraza to be injected, is removed prior to administration of Spinraza.
9. Once drawn into the syringe, if the solution is not used within 6 hours, it must be discarded.
10. Any unused product or waste material must be disposed of in accordance with local requirements.