CADTH

Appendix 4: Previous Spinraza CADTH Canadian Drug Expert Committee Recommendation

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(FINAL)

Nusinersen (Spinraza — Biogen Canada Inc.)
Indication: Treatment of 5q Spinal Muscular Atrophy

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nusinersen be reimbursed for the treatment of 5q Spinal Muscular Atrophy (SMA), if the following criteria and conditions are met:

Criteria:

- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
- Genetic documentation of two copies of the survival motor neuron 2 (SMN2) gene.
- Disease duration less than 26 weeks with onset of clinical signs and symptoms consistent with SMA after the first week after birth and on or before 7 months of age.
- Patient is not currently requiring permanent invasive ventilation.
- Treatment should be discontinued if, prior to the fifth dose or every subsequent dose of nusinersen:
  - there is no demonstrated maintenance of motor milestone function (as assessed using the Hammersmith Infant Neurological Examination [HINE] Section 2); or
  - there is no demonstrated improvement in motor milestone function (as assessed using the HINE Section 2); or
  - if permanent invasive ventilation is required.

Conditions:

- Substantial reduction in price.
- Under the care of a specialist with experience in the diagnosis and management of SMA.
- Collection of real-world evidence on the use of nusinersen for the treatment of SMA.

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Conditions

- Substantial reduction in price.
- Under the care of a specialist with experience in the diagnosis and management of SMA.
- Collection of real-world evidence on the use of nusinersen for the treatment of SMA.

Reasons for the Recommendation

1. In one randomized, double-blind, sham controlled, phase III clinical trial (ENDEAR, N = 121), patients up to seven months of age with diagnosed infantile-onset SMA (duration of disease 0 to 26 weeks) and two copies of the SMN2 gene, had improved motor milestone development with nusinersen compared with sham procedure (between-group difference in the percentage of HINE Section 2 responders of 50.7% [95% CI, 31.8% to 66.5%]), and a lower risk of death or permanent ventilation (39% versus 68%, hazard ratio 0.53 [95% CI, 0.32 to 0.89]). Patients were not eligible for inclusion in the ENDEAR trial if they had signs and symptoms of SMA present at birth or within the first week after birth. No patients in the ENDEAR study required permanent ventilation at baseline.
2. SMA is a rare, genetic, life-threatening, and seriously debilitating neuromuscular disorder that has a heavy burden on caregivers and the health care system. There is an absence of clinically effective drug and non-drug alternative treatments.
3. Based on clinical expert opinion and in consideration of prioritizing patients most likely to benefit from nusinersen, use of nusinersen should be preferentially directed toward patients with SMA who have demonstrated objective improvement in motor outcomes and deferral of permanent mechanical ventilation. In the ENDEAR trial, 36 out of 73 patients (49%) receiving nusinersen were not considered motor milestone responders, and 18 out of 80 (23%) required permanent ventilation.
4. CADTH Common Drug Review (CDR) reanalysis of a cost-utility model submitted by the manufacturer found that nusinersen was unlikely to be cost-effective at the submitted price, with costs per quality-adjusted life-year (QALY) of $9.2 million for SMA type I and $24.4 million for SMA type II. Results for SMA type III were uncertain due to lack of appropriate clinical data, but were estimated at $7.4 million per QALY. Under a scenario of a 95% price reduction for nusinersen, incremental cost-utility ratios (ICURs) still exceed $400,000 per QALY.

Of Note

- CDEC noted that the clinical trial meeting the inclusion criteria of the CDR systematic review focused only on one subset of SMA patients (patients likely to develop SMA type I). There was insufficient evidence regarding the efficacy and safety of

nusinersen in other patient populations, including patients with symptom onset at birth or within one week of birth, patients with advanced SMA who require ventilation, patients older than seven months of age, patients with more than two copies of the SMN2 gene, patients diagnosed at later stages of disease, and patients who are pre-symptomatic. The clinical and cost-effectiveness of treatment with nusinersen in such scenarios is unknown, and there is a lack of data to assess the efficacy and safety of continued use of nusinersen over the long term, regardless of patient population.

- Given that some patients do not respond to treatment with nusinersen, CDEC discussed the importance of criteria to allow for the assessment of whether to continue treating a patient with nusinersen after a specified duration of time. The committee recognized that maintenance of motor function may be considered a meaningful response to treatment in some patients, whereas an improvement in motor functioning may be desirable in others. CDEC recognized that motor function **or** the need for permanent invasive ventilation may necessitate a decision to discontinue treatment with nusinersen. The committee noted that there are several reasons for, and types of, respiratory support (e.g., invasive or non-invasive ventilation, nighttime versus daytime ventilation), and considered that patients requiring a permanent, invasive form of ventilation should be discontinued from treatment with nusinersen given that ventilation is unlikely to be reversible and there is no evidence that nusinersen is efficacious in such patients. A minimum of six months of treatment with nusinersen was considered by the committee to be a sufficient duration to assess the appropriateness of continuing a patient on nusinersen based on their response to treatment. At six months, patients would be old enough for the treating physician to perform an assessment of motor function, and the timing would equate to the approximate timing of administration of the fifth dose of nusinersen according to the Health Canada – approved recommended dosing regimen. No patients in the ENDEAR trial required permanent ventilation at baseline, and as a co-primary efficacy end point in the trial, permanent ventilation was defined as the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event, or if the patient required tracheostomy.

Discussion Points

- CDEC discussed the challenge of recommending reimbursement criteria for nusinersen on the basis of SMA subtype (i.e., SMA type I, II, III, or IV) considering that there is overlap between SMA subtypes on some criteria, and that the achievement of major motor milestones such as sitting or walking independently is both a goal of treatment and a criterion used for classifying patients. SMA subtype is a classification that is often applied retrospectively, and the committee considered the clinical features of SMA (i.e., SMN2 copy number, disease duration, age of onset of clinical signs and symptoms) as more informative for reimbursement recommendations.
- CDEC noted that one phase III randomized, sham-controlled trial (CHERISH, N = 126) was conducted that included patients aged 2 to 12 years, who had onset of clinical signs and symptoms consistent with SMA at >6 months of age, and who could sit independently but had never had the ability to walk independently. Nusinersen was administered as three loading doses (Days 1, 29, and 85) and one maintenance dose at day 274, an administration schedule that differed from the Health Canada – approved recommended dosing schedule. Although the results of this trial demonstrated that nusinersen-treated patients exhibited a statistically significant gain in motor function compared with patients in the sham control group, there was no evidence to confirm that similar efficacy and safety results would be found if nusinersen was given at the Health Canada–approved recommended dosing regimen in this patient population.
- CDEC discussed the exploratory subgroup analysis in the ENDEAR trial that reported efficacy results for patients with a disease duration of less than and equal to 12 weeks, the median of the study population, and those patients with a disease duration greater than 12 weeks. The results of these subgroup analyses were suggestive of preferential responses in patients treated earlier in the course of their disease, and were supported by clinical experts consulted by CADTH who noted that treating early in the disease, specifically for patients who are likely to develop SMA type I, is important. CDEC noted that the variability between practice centres, including urban and rural centres, and the availability of specialists, may impact the timing of diagnosis, as many patients who are likely to develop SMA type I appear normal at birth. Newborn screening programs that include screening for SMA may allow patients to be identified early; late diagnosis is often associated with the need for respiratory support.

Background

Nusinersen has a Health Canada–approved indication for the treatment of patients with 5q SMA. Nusinersen is an antisense oligonucleotide that is administered via intrathecal injection by lumbar puncture. The Health Canada–approved dosage is a 5 mL solution containing 12 mg of nusinersen, with a regimen of four loading doses at day 0, day 14, day 28, and day 63, and subsequent maintenance doses every four months.

Summary of CDEC Considerations

The committee considered the following information prepared by the CDR: a systematic review of randomized controlled trials (RCTs) of nusinersen and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience treating patients with SMA, and patient group-submitted information about outcomes and issues important to patients and caregivers who are affected by SMA.

Patient Input Information

Three patient groups (Muscular Dystrophy Canada [MDC], the Canadian Organization for Rare Disorders [CORD], and Cure SMA Canada) responded to the call for patient input for this CDR review in the form of one submission from MDC and a joint submission from CORD and Cure SMA Canada. Information for the MDC submission was gathered through interviews with 123 SMA patients and 350 caregivers. Information for the initial CORD and Cure SMA Canada submission was gathered from one focus group, four structured interviews, and 247 responses to an online survey. The following is a summary of key input from the perspective of the patient groups:

- The majority of respondents (60%) were considered SMA type II, and reported, most commonly, not being able to walk, suffering from major muscle weakness, pain and fatigue, difficulty with fine motor skills, deep breathing, swallowing, and feeding as part of living with the disease.
- The level of disability caused by SMA places a significant and impactful burden on families and caregivers of patients suffering from the disease. The time and physical support required by patients have substantial financial, psychological, and emotional consequences on families and caregivers.
- Until nusinersen there was no available treatment for SMA. A variety of supportive therapies (e.g., mechanical aids, rehabilitation services, or supportive medications) have typically been used to manage the symptoms, however, patients would still continue to deteriorate on these therapies.
- Patients would like a treatment that would help them regain some range of motion, slow the deterioration process, maintain muscle strength, reduce their dependency on others, decrease respiratory issues, and provide an overall improved quality of life.
- Patients that received nusinersen indicated positive experiences, improvements in muscle strength, and better respiratory function. The greatest concerns expressed by both groups related to access to the drug (i.e., affordability, complex administrative procedures, and the travel required to obtain treatment).

Clinical Trials

The CDR systematic review included one phase III multi-centre, randomized, double-blind, sham- controlled study (ENDEAR; N = 121). The ENDEAR study recruited patients up to 7 months of age with infantile-onset SMA with documented 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote, and two copies of the SMN2 gene. The study excluded patients who had signs or symptoms of SMA at birth or within the first week after birth, patients with hypoxemia, and patients that had a condition that would interfere with the lumbar puncture procedures. Patients enrolled in the ENDEAR trial were randomized in a 2:1 ratio to receive 5 mL intrathecal solution containing 12 mg of nusinersen (n = 81) or to undergo sham procedure (n = 40). The administration of nusinersen and the sham procedure were conducted on study days 1, 15, 29, 64, 183, and 302. The ENDEAR study assessed two co-primary outcomes: motor milestone responders according to the HINE Section 2 tool, and time to death or

permanent ventilation. Originally, the duration of the ENDEAR study was planned to be 13 months. However, the study was concluded early (approximately 6 months after the last patient enrolled) due to positive results in the pre-planned interim analysis.

At the time of the final analysis, 33% of patients in the nusinersen group had completed the follow-up period and 66% had received at least five doses of nusinersen.

The main limitation of ENDEAR was the early termination of the trial which resulted in a loss of data and a shorter time period to assess the efficacy and safety of nusinersen. These two factors may have also contributed to a lack of statistical power necessary to capture differences in the secondary outcomes and subgroup analyses. The use of a non-intention-to-treat (non-ITT) population for the primary analysis, the lack of appropriate control for multiple statistical testing, and the potential for inadvertent unbinding of the investigator were additional limitations that may have had an impact on the interval validity of the ENDEAR trial.

Additional studies assessing the efficacy of nusinersen that did not meet the inclusion criteria of the CDR systematic review included two phase II, single arm trials (NURTURE and CS3A) and one phase III RCT (CHERISH). NURTURE (ongoing, N = 20) was a phase II, single arm trial for patients with pre-symptomatic SMA who had two or three copies of the SMN2 gene, CS3A (ongoing, N = 21) was a phase II, single arm trial in patients with symptoms suggestive of SMA type I, and CHERISH (N = 126) was a phase III randomized, sham- controlled trial for patients with symptoms suggestive of SMA type II. These studies were excluded due to study design (NURTURE and CS3A), and due to a dosing regimen that did not match the Health Canada–approved regimen (CHERISH and CS3A). Two other studies not considered in the CDR clinical review included CS2 and CS12. CS2 was a phase I, open-label, dose-escalation study aimed to assess the pharmacodynamics and pharmacokinetics of multiple nusinersen doses. CS12 was an open-label, single arm, extension study of patients who had completed one of two phase I trials. The primary aim of CS12 was to report on tolerability and clinical laboratory parameter changes during the study. These two studies were not included in the CDR review due to their study design, differences in dosing and administration regimen, and lack of relevant primary outcomes.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- Motor function-related outcomes: This was presented in the ENDEAR study through the first co-primary outcome of proportion of motor milestone responders (Section 2 of the HINE). A responder was defined as: “(i) The patient demonstrated at least a 2-point increase in the motor milestone category of ability to kick or achievement of maximal score for that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND (ii) among the seven motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening.” Additional related secondary outcome reported in the ENDEAR was the proportion of Children’s Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders, in which a responder was defined as a patient with a score change from baseline of 4 or greater points when assessed on study days 183, 302,
or 394.
- Respiratory and survival-related outcomes: This was presented in the ENDEAR study through the second co-primary outcome of time to death or permanent ventilation. In addition, two related secondary outcomes of survival rate and the percentage of patients not requiring permanent ventilation were assessed. The ENDEAR study defined the outcome of permanent ventilation as “the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event”, or if the patient required tracheostomy.

No health-related quality of life or caregiver burden measures were assessed in the ENDEAR study.

Efficacy

The final efficacy analysis demonstrated a statistically significant difference in the proportion of HINE Section 2 motor milestone responders between the nusinersen treatment group and the sham procedure control group where 37 patients out of 73 in the nusinersen group (51%) compared with 0 patients out of 37 in the sham procedure control group were classified as responders (difference in percentage = 50.7, 95% CI, 31.8 to 66.5). The captured improvement in motor milestones of patients was also supported by a second motor milestone measure, the CHOP INTEND, where 71% of the patients allocated to nusinersen treatment achieved an improvement of 4 or more points on the CHOP INTEND scale as compared with 3% in the sham procedure control

group (percentage difference = 68.53, 95% CI, 51.27 to 81.99). The definition of treatment responders has been noted in the Health Canada Reviewer Report to be broad in that it captures many patients with minimal improvement, and treats those patients in a similar way to those who gained more significant improvements.

The second co-primary composite outcome in the ENDEAR study – time to death or permanent ventilation – indicated that 31 patients (39%) in the nusinersen group died or required permanent ventilation versus 28 patients (68%) in the sham procedure group during a period of roughly approximately 13 months (hazard ratio (HR) = 0.53, 95% CI, 0.32 to 0.89). When each event (death, and permanent ventilation) was analyzed as a separate outcome, the results indicated a statistically significant difference between nusinersen group and the sham procedure in overall survival (HR = 0.37, 95% CI, 0.18 to 0.77), but not in time to permanent ventilation (HR = 0.66, 95% CI, 0.32 to 1.37).

An exploratory subgroup analysis based on the median disease duration of 12 weeks (less than and equal to 12 weeks, and greater than 12 weeks) found a statistically significant difference between nusinersen and sham-treated patients for HINE Section 2 motor milestone responders in both groups. For time to death or permanent ventilation, the subgroup analysis based on median disease duration showed statistically significant differences compared with the sham procedure group in the subgroup below the median disease duration (HR = 0.24, 95% CI, 0.10 to 0.58) but failed to show statistically significant differences in the subgroup over the disease median duration (HR = 0.84, 95% CI, 0.43 to 1.67). However, due to the non-significance of a prior outcome in the stage-wise hierarchical strategy, (percentage of patients not requiring permanent ventilation) all subgroup analyses are considered exploratory.

Harms (Safety and Tolerability)

- Adverse events were reported in 96% of patients in the nusinersen group and 98% in the sham control group. Most adverse events and serious adverse events were related to infections and respiratory related complications. None of the adverse events were considered related to the study treatment by the study investigators.
- A lower percentage of patients in the nusinersen group had a serious adverse event compared with the sham control group (nusinersen versus control: 76% versus 95%).
- All withdrawals due to adverse events were due to the death of the patient. There were numerically fewer withdrawals due to adverse events in the nusinersen group (16%) versus the control group (39%).
- There were 16 deaths (39%) reported in the control group versus 13 deaths (16%) reported in the nusinersen group. Deaths attributed to respiratory, thoracic, and mediastinal disorders were the highest proportion in both groups (9% in the nusinersen group and 29% in the control group).
- Vomiting was noted in the nusinersen group as related to the lumbar puncture procedure (5% in nusinersen group, 0% in the control group). Two patients (3%) in the nusinersen treatment arm were reported as having an adverse effect related to renal and urinary disorders, compared with one patient (2%) in the control group.

Cost and Cost-Effectiveness

Nusinersen is available as a single-use solution in a 5 mL vial size (12 mg) at a marketed price of $118,000 per vial. The recommended dose is: initial treatment with four loading doses, with the first three loading doses administered at 14-day intervals (day 0, day 14, and day 28), and a final loading dose approximately 30 days after the third loading dose (day 63); maintenance treatment is 12 mg every 4 months. The annual cost of treatment with nusinersen in the first year is $708,000 and decreases to $354,000 for maintenance treatment (3 doses) in subsequent years.

The manufacturer submitted three cost-utility analyses for SMA type I, II, and III. Each analysis was based on a Markov state-transition model comparing nusinersen with current standard of care (or real-world care [RWC] which includes supportive symptomatic treatment of respiratory, nutritional, and orthopedic function decline) for patients with q5 SMA. The analyses were conducted form the health care system perspective, with costs and outcomes discounted at 1.5% per annum.

In the SMA type I model, health states included baseline clinical status; whether clinical status improved, worsened, or had no improvement; milestones consistent with SMA type II (e.g., sits without support, stands with assistance, walks with assistance and stand/walks unaided); and, death. The analysis was conducted over a time horizon of 25 years. Transition probabilities relating to disease progression and mortality within the first thirteen months were derived from the ENDEAR study. Subsequent probabilities were based on assumptions.

In the SMA type II model, health states included baseline clinical status; whether clinical status worsened, had no improvement, had mild improvement, or had moderate improvement; whether the patient can stand/walk with assistance and milestones consistent with SMA type III (e.g., stand unaided and walks unaided); and, death. The analysis was run over a time horizon of 50 years. Transition probabilities relating to disease progression and mortality within the first fifteen months were derived from the CHERISH study. Subsequent probabilities were based on assumptions.

In the SMA type III model, health states included: non-ambulatory, ambulatory, and death. The analysis was run over a time horizon of 80 years. For treatment with nusinersen, transition probabilities relating to disease progression within the first 24 months were derived from the CS2+CS12 study. Subsequent probabilities were based on assumptions. For RWC, patients were assumed to maintain ambulatory status.

The manufacturer reported ICURs for nusinersen compared with RWC as follows: for SMA type I, $665,570 per QALY; for SMA type II, $2.1 million per QALY; and, for SMA type III, $2.9 million per QALY. The manufacturer indicated the probability that nusinersen was cost-effective assuming a willingness to pay of $300,000 per QALY was 0% for all SMA types.

CDR identified the following primary limitations with the manufacturer's economic model:

- In the design of the economic model for SMA type I and II, health states are relative states which are characterized by the patient's baseline status. In economic modelling, it is desirable that states are absolute states which relate to the level of functioning at that time, not relative to previous functioning.
- Utility values for the SMA type I and SMA type III models were derived from an unpublished analysis provided for Biogen Idec, and for the SMA type II model based on an unpublished mapping exercise. A number of issues were identified with these approaches, including that the valuation process was not appropriate, and that the health states that were valued were not specific.
- Assumptions within the manufacturer's submission relating to disease progression for patients with SMA type I, II, and III receiving nusinersen post the time frame of the clinical studies, and mortality for patients with SMA type I and II being based on milestones reached, were unfounded and biased in favour of nusinersen.
- A clinical expert consulted by CDR for this review raised a number of concerns regarding the clinical trial data for nusinersen that limit the inferences and generalizations that can be made from the economic evaluation. For example, the population that may receive nusinersen is not reflected in the clinical trials and there is a lack of comparative clinical trial data for SMA type III. While analyses were conducted by SMA type (i.e., for types I and II), further stratified analysis by clinical features would be desirable.

CDR was able to conduct reanalysis to address the limitations identified regarding: choice of utility values, assumptions for disease progression, and mortality. The CDR reanalysis was aligned with the manufacturer's findings that nusinersen was not cost-effective for any of the three SMA types; however, CDR reanalysis reported much higher incremental costs per QALY estimates: $9.2 million for SMA type I and $24.4 million for SMA type II. Results for SMA type III should be considered speculative, given the concerns raised due to the lack of appropriate clinical data. Analysis based on the limited data available concluded nusinersen was unlikely to be cost-effective with an incremental cost per QALY of $7.4 million for SMA type III. For each SMA type, the probability that nusinersen was cost-effective at a willingness-to-pay threshold of $500,000 remained 0%.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 15, 2017 Meeting

Regrets

None

Conflicts of Interest

None