CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated December 20, 2017.

NUSINERSEN (SPINRAZA — BIOGEN CANADA INC.)
Indication: Treatment of 5q spinal muscular atrophy.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that nusinersen be reimbursed for the treatment of 5q spinal muscular atrophy (SMA), if the following conditions are met:

Conditions for Reimbursement

Initiation Criteria
1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
2. Patients who:
   - 2.1. are pre-symptomatic with two or three copies of SMN2, or
   - 2.2. have had disease duration of less than six months, two copies of SMN2, and symptom onset after the first week after birth and on or before seven months of age, or
   - 2.3. are 12 years of age or younger with symptom onset after six months of age, and never achieved the ability to walk independently.
3. Patient is not currently requiring permanent invasive ventilation.

Administration Criteria
1. A baseline assessment using an age-appropriate scale (the Hammersmith Infant Neurological Examination [HINE] Section 2, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND], or Hammersmith Functional Motor Scale-Expanded [HFMSE]) must be completed prior to initiation of nusinersen treatment.
2. Patient must be under the care of a specialist with experience in the diagnosis and management of SMA.

Renewal Criteria
1. Treatment should be discontinued if, prior to the fifth dose or any subsequent dose of nusinersen:
   - 1.1. there is no demonstrated achievement or maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were pre-symptomatic at the time of treatment initiation; or
   - 1.2. there is no demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were symptomatic at the time of treatment initiation; or
   - 1.3. permanent invasive ventilation is required.

Pricing Condition
1. Reduction in price.

CADTH

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

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Reasons for the Recommendation

1. In one phase II, ongoing, single arm, non-comparative study (NURTURE; N = 25), which enrolled pre-symptomatic SMA patients with a mean age at nusinersen first dose of 21 days and who had two or three copies of the SMN2 gene, [redacted]. Patients treated with nusinersen also exhibited an overall increase in motor milestones achieved after six months of treatment: [redacted]. Overall, results from NURTURE suggested benefit from treatment of pre-symptomatic patients.
2. In one phase III, double-blind randomized clinical trial (RCT) (ENDEAR, N = 121), patients up to seven months of age with diagnosed infantile-onset SMA (duration of disease zero 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% confidence interval (CI), 31.8% to 66.5%]), as well as a lower risk of death or permanent ventilation (39% versus 68%, hazard ratio 0.53 [95% CI, 0.32 to 0.89]).

3. In one phase III, double-blind RCT (CHERISH, N = 126) with patients aged two to 12 years at randomization who had symptom onset after six months of age, and who could sit independently but had never had the ability to walk independently, and of whom 88% had three copies of the SMN2 gene, there was a statistically significant improvement in the change in HFMSE score from baseline to month 15 in patients in the nusinersen group compared with the sham control group. The least squares mean (LSM) increase from baseline in HFMSE score in the nusinersen group was four points compared with a decrease of 1.9 points in the sham control group at 15 months (LSM difference = 5.9 [95% CI, 3.7 to 8.1]). The HFMSE response (≥ 3 point increase) at 15 months was higher in the nusinersen group (56.8%) compared with the sham control group (26.3%).
4. SMA is a rare, genetic, life-threatening, and seriously debilitating neuromuscular disorder that has a heavy burden on patients, caregivers and the health care system. There is an absence of approved clinically effective drug and non-drug alternative treatments.
5. Based on clinical expert opinion and in consideration of identifying patients most likely to benefit from nusinersen, use of nusinersen should be 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.
6. 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 still exceed $400,000 per QALY.

Implementation Considerations

- A motor milestones responder is based on the definitions used in the NURTURE, ENDEAR, and CHERISH studies.
  - Responders based on the motor milestones categories in Section 2 of the HINE (with the exclusion of voluntary grasp) are as follows:
    - The patient demonstrated at least a two-point increase from treatment initiation in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a one-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND
    - Among the seven motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined previously) in more categories than worsening. Worsening for the category of ability to kick is defined as at least a two-point decrease or decrease to the lowest possible score of no kicking. Worsening is defined as at least a one-point decrease for the other six categories.
  - Responders based on the CHOP INTEND are those with a score change from treatment initiation of four or more points.
  - Responders based on the HFMSE are those achieving a three-point or greater increase from treatment initiation to 15 months of treatment.
  - The HINE is intended for infants aged two to 24 months. The CHOP INTEND is intended for children aged approximately four months to four years. The HFMSE is intended for individuals aged two years and older.

- Given the extraordinarily high cost of nusinersen, the budget impact of using nusinersen will be considerable, even if the price is reduced substantially. Therefore, the reimbursement conditions reflect the importance to CDEC of identifying those patients with SMA who are most likely to benefit from treatment.

Discussion Points

- The results of NURTURE and ENDEAR were suggestive of preferential responses in patients treated earlier in the course of their disease, and were supported by clinical experts consulted by CDR who noted that treating early in the disease, especially 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.

- The highest quality evidence with respect to the magnitude of the treatment effect with nusinersen would be in the patient populations identified by the NURTURE, ENDEAR, and CHERISH studies. The remaining study designs assessing nusinersen efficacy and safety that were reviewed as part of this submission contained substantial limitations that impacted the validity of those results.
- 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 most patients (96%) included in CHERISH had two or three copies of SMN2, while three patients had four copies (SMN2 copy number was unknown for two patients). Approximately one-third of patients included in CHERISH were able to walk with support.
- There is insufficient evidence from clinical trials regarding the efficacy and safety of nusinersen in patients with mild SMA symptoms, patients older than 12 years of age, patients with three copies of the SMN2 gene who are able to walk unaided, patients with four copies of the SMN2 gene (including patients with adult onset SMA [SMA type IV]), and patients who have advanced SMA and require ventilation. Likewise, there remains limited evidence for the long-term efficacy and safety of nusinersen in all patients with any number of copies of the SMN2 gene. Additional research in this regard, including collection of real-world evidence on the use of nusinersen for the treatment of SMA, is needed.
- CDEC discussed the limited amount of evidence from the NURTURE, ENDEAR, and CHERISH studies for patients with SMA who have symptom onset after seven months of age and those younger than two years of age who have two copies of the SMN2 gene, and for those older than six weeks of age and younger than two years of age with more than two copies of the SMN2 gene. The committee noted that these limitations in the design of the studies should not exclude these patients from the reimbursement population for nusinersen.
- CDEC heard clinician expert input that the decision to continue treatment with nusinersen would be based on achieving a response with therapy (i.e., maintaining or improving motor milestones relative to baseline assessments) and ventilation status. CDEC also heard expert input that assessments of response to treatment at discrete time points may be affected by factors other than the underlying disease.

Background

This resubmission for nusinersen is for the same previous 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 dose 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.

Submission History

Nusinersen was previously reviewed for the treatment of patients with 5q SMA and received a recommendation of reimburse with criteria and conditions. The original CDR systematic review of nusinersen included one randomized, double-blind, sham-controlled, phase III clinical trial (ENDEAR, N = 121) where patients up to seven months of age with diagnosed infantile-onset SMA (duration of disease of zero 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]). The recommendation was based on the aforementioned evidence presented in the original CDR report of nusinersen. CDEC identified the following areas as constituting an evidence gap: 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 manufacturer provided this resubmission with additional data and information from ongoing and recently conducted studies that was not available during the

original submission. In light of the new information, this resubmission has been conducted with the primary goal of attempting to provide and assess any clinical studies that can fill the evidence gaps identified by CDEC.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of clinical studies of nusinersen and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with 5q SMA, and patient group–submitted information about outcomes and issues important to patients and caregivers who are affected by SMA.

Summary of Patient Input

Two submissions from patient groups were received. For this review, Muscular Dystrophy Canada used its previous submission as a base and conducted an additional survey of patients and caregivers (388 responses) in July and August 2018. The Canadian Organization for Rare Disorders and Cure SMA Canada responded with one joint submission; the groups referenced their original submission (with data gathered from one focus group, four interviews, and a survey with 247 responses) and for this submission also conducted semi-structured interviews in August of 2018 with 11 families of patients with nusinersen experience. The following is a summary of key input from the perspective of the patient groups:

- Depending on the severity of the condition, the patient group surveys found significant proportions of respondents with major problems or inability in each of the following areas: walking, muscle strength (weakness, pain, or fatigue), fine motor skills, (deep) breathing, and swallowing or feeding. Inability to walk means relying on wheelchairs and other mobility aids and dealing with associated barriers. Assistance may be required to transfer to and from mobility aids. Those who can walk with assistance may not be able to get up, use the stairs, bathe, or use the toilet independently. Young patients also miss out on typical childhood experiences such as using the playground. In more severe cases, patients cannot execute basic movements such as sitting up or rolling, and require help with needs (such as transfers), as well as positioning in wheelchairs and in beds. Breathing problems often require the use of mechanical ventilation aids such as BiPap.
- SMA type I is often the most severe and is the most common genetic cause of infant mortality.
- 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.
- Of the 11 patients interviewed who have experience with nusinersen, patients with SMA type I reported noticeable improvements in core physical abilities — namely, sitting, rolling over, standing, using a walker, and walking. Patients with SMA type II reported improvements in physical and motor activities, breathing, eating, talking, illness, and recovery, and with regard to the impact on families and the social and health systems. Patients with SMA type III reported improvements in their level of mobility and independence.

Clinical Trials

The systematic review included 15 studies; as part of the resubmission of nusinersen to CADTH, the manufacturer provided 19 reports representing data from 10 nusinersen development studies, two observational studies, and one letter from a clinical centre for SMA. Of the 10 nusinersen development studies, three were randomized controlled trials (ENDEAR [N = 121], CHERISH [N = 126], and EMBRACE [N = 27]), four were phase I uncontrolled trials along with their extension studies (CS1 [N = 28], CS2 [N = 34], CS10 [N = 18], and CS12 [N = 47]), two were phase II uncontrolled trials (CS3A [N = 21], and NURTURE [N = 25]), and one was an extension study that included participants from all trials except EMBRACE and NURTURE (SHINE [N = 207]). Further to the previously mentioned studies, the CDR systematic search identified three case series observational studies that outlined the experience with expanded access programs in several countries for patients diagnosed with SMA. These three observational studies

regarding the expanded access program focused on nusinersen treatment for patients with SMA type I but did not restrict the patients' age below seven months.

NURTURE targeted patients who were pre-symptomatic, had two or three copies of the SMN2 gene, and were six weeks of age or younger. CS3A targeted patients who were between 21 days and seven months of age, and presented symptoms at or before six months of age. CS3A had no restriction over SMN2 gene copy number. ENDEAR targeted similar patients as CS3A with the added inclusion criterion of having two SMN2 gene copies. CHERISH targeted patients who were between the ages of two and 12 years, could sit independently, were never able to walk, and presented symptoms after six months of age. EMBRACE included patients who were not eligible for ENDEAR or CHERISH; specifically, patients with disease onset at six month or earlier who have three SMN2 gene copies, patients with disease onset at six months or earlier who are over seven months of age and have two SMN2 gene copies, and patients with disease onset after six months who have two SMN2 gene copies. CS1 and CS2 targeted patients aged two to 15 years with no specification regarding disease onset. The exclusion criteria of these studies were similar in that they excluded patients in need of ventilator support, presence of a condition that would interfere with the nusinersen administration, and previous exposure to other investigational drugs. In addition, CHERISH excluded patients who have active gastric tube feeding.

The nusinersen extension studies (CS10, CS12, and SHINE) included patients who satisfactorily completed the primary study. The three case series of expanded access included patients with a diagnosis of SMA type I. Two case series addressed adult patients with SMA undergoing nusinersen treatment.

The included single arm studies share a common limitation pertaining to the study design: the lack of a control group to draw a statistical causal inference. Without a control group, it is difficult to attribute any benefit observed to nusinersen alone, as other confounding factors are potentially present. In addition, while objective clinical outcomes, such as death or need for ventilation, may have less potential to be biased by the open-label design of the study, other more subjective outcomes may be biased. More specific limitations are present in these studies beyond the single arm design; NURTURE is an ongoing trial and the interim results presented here may not reflect the final planned analysis of the predefined end point, also considering that for some outcomes, not all patients were assessed and this missing data might affect the outcome. SHINE is also an ongoing extension study and the interim results may be confounded by the dropouts and missing data from the original trials. Also, the inclusion of patients who participated in dose-finding studies resulted in a heterogeneous population in terms of drug exposure, further reducing CDR's ability to extrapolate observed results into the Canadian population undergoing Health Canada–indicated dosages.

Of the three included double-blind, randomized, sham-controlled trials, 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. EMBRACE was a small, exploratory, phase II trial that showed significant imbalances in the baseline characteristics of randomized patients and was terminated prematurely. CHERISH had a main limitation of using a nusinersen dosage schedule that is different from Health Canada's recommended dosing schedule.

The five included observational, non-comparative, case series studies share a common limitation pertaining to the study design: the study design is descriptive in nature and cannot draw any association between an observed potential benefit and nusinersen treatment. The value of any observed benefits as compared with baseline is limited, as no measure was taken to control for any potential confounders or natural disease fluctuations, and such results can only be used for hypothesis generation. Two of these studies were addressing SMA in adult patients; both of them further suffer from important limitations in reporting pertinent information and data regarding the patient population and outcome, and thus were unable to provide evidence of nusinersen efficacy in adult patients with SMA.

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 included studies based on the population assessed as the HINE Section 2 infantile population, the HFMSE child population, and/or the CHOP INTEND population. Other motor function outcomes included the World Health Organization motor development milestones, the six-minute walking test (6MWT), and the Upper Limb Module test.
- Respiratory and survival-related outcomes: These were presented in the NURTURE and ENDEAR studies as time to death or permanent ventilation. 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 a tracheostomy.
- Health-related quality of life measures: This outcome was presented in the CHERISH study as an exploratory outcome using the Pediatric Quality of Life Inventory (PedsQL) and Accreditation Council for Education in Nutrition and Dietetics tools.

Efficacy

The original CDR submission covered the ENDEAR study; the final efficacy analysis of the ENDEAR study 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 zero patients out of 37 in the sham procedure control group were classified as responders (per cent difference = 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 four 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 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 the 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.

The CDR systematic review of this resubmission presented evidence addressing the evidence gaps identified by CDEC in its original recommendation for nusinersen.

Patients Who Are Pre-Symptomatic

Addressing this population was a phase II, single arm trial (NURTURE). [redacted]

[redacted]

Patients with Infantile-Onset SMA, Including Patients with SMN2 Gene Copy Greater Than Two

Addressing this population was the extension study SHINE, which contrasted the assessed outcome to the baseline of patients that originally enrolled in the CS3A phase II, single arm study. [redacted]

Patients with Mixed Infantile and Early Childhood Onset, Including Patients with SMN2 Gene Copy Greater Than Two

Addressing this patient population was a phase II, randomized, sham-controlled, exploratory trial (EMBRACE). [redacted]

Patients with Early Childhood SMA Onset, Including Patients with SMN2 Gene Copy Greater Than Two

Addressing this population was a phase III, randomized, double-blind, sham-controlled trial (CHERISH). The primary outcome, the change in HFMSE score from baseline to month 15, showed a statistically significant and potentially clinical meaningful difference between groups (LSM difference = 5.9 [95%CI 3.7 to 8.1]). This was further supported by a statistically significant difference in the first secondary outcome of HFMSE responders (≥ 3 point increase) at 15 months, showing a difference in proportion of 30.5% (95% CI, 12.74 to 48.31). The second outcome to be tested in the statistical hierarchy (proportion of patients achieving new motor milestones at 15 months) failed to show statistical significance. All reported *P* values in subsequent outcomes are thus not adjusted for multiple testing. Overall, patients in the nusinersen group had a mean of 0.2 new motor milestones achieved (95% CI, 0.1 to 0.3) compared with a mean of –0.2 in the sham control group (95% CI –0.4 to 0). Supporting the positive primary finding, patients in the nusinersen group exhibited a mean improvement of 4.2 (95% CI, 3.4 to 5.0) from baseline in the outcome of Revised Upper Limb Module (RULM) test at 15 months compared with a mean improvement of 0.5 (95% CI, –0.6 to 1.6) from baseline in the sham control group. [redacted] One patient in each group was able to stand alone at 15 months, while only one patient in the study from the nusinersen group was able to demonstrate the milestone of walking with assistance at 15 months.

Patients with Later Childhood Onset, Including Patients with SMN2 Gene Copy Greater Than Two

Addressing this population was the extension study SHINE, which contrasted the assessed outcome to the baseline of patients that originally enrolled in the phase I trials (CS1 and CS2). [redacted]

[redacted]

Adult Patients

Two case series observational studies poster abstracts address this patient population. Unfortunately, no explicit description of the characteristics of the included patients was reported. Elsheikh 2018 observed that three patients reported subjective improvement in stamina and endurance, one patient's HFMSE score did not improve, one patient's HFMSE score improved from 31 to 34, and one patient had an increase of 25 metres in the 6MWT. Day 2018 showed a patient-reported [redacted]

Patients Diagnosed Before Seven Months of Age but Received Treatment after Seven Months of Age

Addressing this population was the SHINE extension study of patients previously enrolled in ENDEAR with the assessment contrasted against SHINE baseline. Additionally, two case series, Pane 2018 and Aragon 2018, also address this patient population. Time to death or permanent ventilation was only reported in the SHINE – ENDEAR index study. At the start of SHINE, [redacted] Aragon 2018 reported a median HINE score of 3.5 (range = 0 to 11) at month six contrasted with the baseline median value of 1 (range = 0 to 6). Pane 2018 reported that the mean change in HINE score was 1.3 (SD = 2.2). CHOP INTEND score in SHINE (ENDEAR index) at last observed visit showed a change of [redacted]. Aragon 2018 reported a median score of 35 (range = 19 to 51) at six months contrasted with the baseline median value of 31.5 (range = 6 to 45). Pane 2018 did not provide a summary measure for this outcome; instead, they reported that the CHOP INTEND changes ranged between –7 and 27 points.

Patients with SMA Who Require Ventilation

Addressing this population was a single, observational, non-comparative, case series of Pechmann 2018. At six months after nusinersen treatment, Pechmann 2018 reported a mean change from baseline of 9.0 (SD = 8.0) points, starting from a mean baseline value of 22.3 to a mean value at assessment date of 31.2 (SD = 16.2). In a subgroup of patients that started the study requiring permanent ventilation (18 patients [30%]), the mean change in the CHOP INTEND score from baseline was 5.6 points (SD 7.5). At six months after nusinersen treatment, Pechmann 2018 reports a mean change in HINE score from baseline of 1.4 (SD 2.1) points, starting from a mean baseline value of 0.8 to a mean value at assessment date of 2.5 (SD 3.3). These results were not reported in the subgroup of patients that started the study requiring permanent ventilation. At the beginning of the study, 26 patients (43%) did not require ventilation; at six months, 19 patients (31%) did not require ventilation. Non-invasive ventilation less than 16 hours per day was required by 17 patients at the start and at the end of the study (28%). The number of patient requiring ventilation > 16 hours per day or to have a tracheostomy increased from 18 (30%) at the beginning of the study to 25 (41%) at the end of the study.

Harms (Safety)

Throughout all of the manufacturer-provided trials, the most common adverse events (AEs) were related to infections and/or respiratory problems, two common complications of SMA. A number of patients (5%) in the nusinersen treatment group experienced vomiting, which was related to the lumbar puncture procedure. A lower percentage of patients reported serious AEs in the nusinersen group (76%) than in the sham procedure group (95%). Extension and long-term safety studies reported a similar safety profile. The Health Canada product monograph suggests that the majority of the reported AEs are related to the disease process or the lumbar puncture procedure.

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 four months. The annual cost of treatment with nusinersen ranges from $354,000 for maintenance treatment (three doses) to $708,000 in the first year (six doses).

As part of the resubmission to CDR, the manufacturer provided new clinical information relating to different subpopulations with SMA. The manufacturer did not, however, provide a revised economic submission, nor did it provide any discussion relating to the new clinical information and how this may impact the findings of the economic review based on the original submission. Thus, the CDR economic review remains unchanged with no further data provided to refute the original issues or limitations identified, or to alter the conclusions of the report.

The manufacturer submitted three cost-utility analyses for SMA types I, II, and II. 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 and/or 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 13 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 and/or walk with assistance and milestones consistent with SMA type III (e.g., stand unaided and walk 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 15 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 incremental cost-effectiveness ratios 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 threshold of $500,000 per QALY was 0% for all SMA types.

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

- In the design of the economic model for SMA types I and II, health states are relative states that are characterized by the patient's baseline status. In economic modelling, it is desirable that states are absolute states that 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; the SMA type II model was based on an unpublished mapping exercise. A number of issues were identified with these approaches, including that the valuation process was not appropriate and 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 past the time frame of the clinical studies; and, mortality for patients with SMA type I and II being based on milestones reached were both unfounded and biased in favour of nusinersen.

- The clinical expert consulted by CDR raised a number of concerns regarding the clinical trial data for nusinersen, which undermines the ability to facilitate the economic evaluation. These include that the population that may receive nusinersen is not reflected in the clinical trials and that a lack of comparative clinical trial data exists for SMA type III. While analysis can be conducted by SMA type (i.e., for types I and II), further stratified analysis by disease status would be desirable. As subgroup analysis of HFMSE responders by age category suggests that nusinersen is effective in those aged under six but not in those aged six and over, stratified cost-effectiveness analysis by age would be highly informative.

CDR was able to conduct reanalysis to address the limitations identified regarding choice of utility values and 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%. The model was not updated to include an analysis of the cost-effectiveness of nusinersen in the pre-symptomatic population and therefore no conclusions could be drawn for this group of patients.

Request for Clarification

The drug plans that participate in the CDR process filed a request for clarification during the embargo period for the CDEC recommendation of nusinersen. The questions posed by the drug plans and responses from CDEC are summarized below.

Can CDEC clarify whether the discontinuation criteria specifically for pre-symptomatic patients are applicable and sufficient?

CDEC intended for there to be criteria in the original recommendation to allow for the assessment of whether continued treatment with nusinersen would be appropriate. However, after further discussion, CDEC acknowledged that the criteria for renewal that were previously presented would not necessarily be relevant to all patient subgroups, particularly the presymptomatic subgroup. Therefore, CDEC has modified the relevant criteria to address this issue as follows:

"Treatment should be discontinued if, prior to the fifth dose or any subsequent dose of nusinersen:

- there is no demonstrated achievement or maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were pre-symptomatic at the time of treatment initiation; or

- there is no demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were symptomatic at the time of treatment initiation; or

- permanent invasive ventilation is required."

As it relates to the pre-symptomatic patient recommendation, some pediatric patients may be identified through other means, besides "newborn screening programs", so can CDEC please clarify whether the reference to this identification method was just an example or the preferred method?

A newborn screening program may be universal, or targeted. A targeted program may be preferred from the point of view of maximizing yield when the screening test is expensive or invasive. However, universal screening may ultimately be adopted based on the objective of early identification of sporadic (non-familial) cases, in which there is potential benefit from treatment with nusinersen. CDEC was not specifying or recommending any particular screening strategy for SMA nor did CDEC assess the benefits and risks of different screening strategies during this review.

CDEC decided to remove "newborn screening programs" as a means of identifying presymptomatic patients with SMA from the Initiation criteria following additional discussion.

Can CDEC please provide clarification on the population of pediatric patients older than 12 years of age, who had disease onset in early childhood and would have met the criteria if nusinersen had been available at the time of their diagnosis. If treatment was initiated in the patients currently older than 12 years of age, who meet the CDEC recommended criteria (i.e. 2-3 copies of SMN2 gene, and never achieved the ability to walk independently, symptom onset after six months of age), are the discontinuation criteria described above still appropriate?

CDEC accepted the evidence from CHERISH as sufficient to support reimbursement despite differences in the dosing regimen used compared to the Health Canada approved dosing schedule. However, patients older than 12 were excluded from the trial. There is an evidence gap in understanding how older patients will respond to nusinersen, particularly given that the outcomes are largely focused on developmental and motor milestones. This is true despite any history of a developmental course that may have supported reimbursement, had the current recommendation been in force at the time. CDEC has no evidence upon which to state those over the age of 12 would or would not benefit from the use of nusinersen and are unable to comment on the potential magnitude of benefit to expect in this patient population, should it be considered effective. CDEC believes the recommended discontinuation criteria provided, in particular if the motor skills at baseline are not maintained and/or the patient progresses to require permanent ventilation, are appropriate for those over 12 years of age.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Ms. Heather Neville, Mr. Allen Lefebvre, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 21, 2018 Meeting (Initial)

Regrets

One CDEC member did not attend.

Conflicts of Interest

None

February 20, 2019 Meeting (Reconsideration)

Regrets

One CDEC member did not attend.

Conflicts of Interest

None