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CADTH Reimbursement Recommendation

Nusinersen (Spinraza)

Indication: Patients with type II and type III SMA who are older than 18 years of age regardless of ambulatory status

Sponsor: Biogen Canada Inc.

Final recommendation: Do not reimburse

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Spinraza?

CADTH recommends that Spinraza should not be reimbursed by public drug plans for the treatment of patients with type II and type III 5q spinal muscular atrophy (SMA) regardless of ambulatory status if initiated in patients older than 18 years of age.

Why Did CADTH Make This Recommendation?

- No randomized clinical trials evaluating the efficacy or safety of Spinraza in treatment-naïve adult patients with type II or type III SMA have been conducted.
- Evidence from 4 observational studies generally suggested that treatment with Spinraza may improve or maintain physical abilities; however, due to the limitations of these studies, it was not possible to conclude that the improvement or maintenance in physical function including movement or strength were a result of Spinraza.
- There is a need for treatments in adult patients with type II and type III SMA that stabilize disease progression, including the avoidance of using machines to help breathing, improve strength in the upper limbs, and improve health-related quality of life (HRQoL). However, the evidence reviewed did not show that Spinraza would meet any of these needs.

Additional Information

What Is SMA?

SMA is a rare, severe genetic disease that occurs in 1 in 10,000 live births and is the leading genetic cause of infant death. SMA results in the breakdown and loss of specialized nerve cells, called motor neurons that control muscle movement due to a shortage in the survival motor neuron (SMN) protein. The loss of motor neurons results in weakness and loss of muscles, mostly those that are needed to stand and sit, and move the arms and legs.

Unmet Needs in SMA

There is a need for treatments for adults with SMA that offer stability and improved HRQoL through greater independence, improved strength (primarily in the arms and respiratory function), and halting of disease progression. Patients may also benefit from treatments that are easier to take, have fewer side effects, and are easier to access.

How Much Does Spinraza Cost?

Treatment with Spinraza is expected to cost approximately $708,000 per patient per year in the first year, and $354,000 per patient per year in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nusinersen not be reimbursed for the treatment of type II and type III SMA regardless of ambulatory status if initiated in adult patients older than 18 years of age.

Rationale for the Recommendation

No randomized clinical trials evaluating the efficacy or safety of nusinersen in treatment-naïve adult patients with type II or type III SMA were available; the best available evidence for this review was from 4 non-comparative, observational studies (Hagenacker et al., Maggi et al., EU Registry Study, and Pera et al.). Although the studies generally suggested that treatment with nusinersen had a positive effect on motor function (measured by the Hammersmith Functional Motor Scale Expanded [HFMSE], Revised Upper Limb Module [RULM], and 6MWT), key limitations including the uncontrolled nature of the studies, large amounts of missing data, relatively short duration of follow-up for a chronic disease, and high degree of selection bias resulted in a patient population that was not considered representative of adult patients with SMA in Canada, and a treatment effect that could not be solely attributed to the intervention. In addition, several potential confounders were identified that may impact motor function, such as prescribed physical activity (which maintains neuronal connectivity and muscle function) and potential learning and training effects for functional outcomes scales. The clinical experts described the known natural history of type II and III SMA in adults as that of a chronic progressive neurodegenerative disease with temporal variability and substantial heterogeneity in the degree of disability and motor function over time. Therefore, CDEC could not draw any conclusions that the changes or maintenance in motor function scores were a result of nusinersen administration due to the considerable uncertainty associated with the evidence.

CDEC acknowledged that there is currently an unmet need for disease-modifying treatment options in adults with type II and type III SMA. CDEC noted that this unmet need is primarily in adult patients who did not have treatments available as young adults or earlier. Individuals eligible to initiate treatment as pediatric patients may be eligible to continue into adulthood. Patients and caregivers identified a need for treatments that stabilize disease progression, improve HRQoL through greater independence, and improve strength (primarily in the arms and respiratory function). The committee was unable to conclude, from the available evidence, that nusinersen would meet these unmet needs or provide any clinically meaningful benefits in adults with type II or III SMA, regardless of ambulatory status.

Discussion Points

- CDEC reviewed and considered the input from patients and clinician groups and acknowledges that there is a substantial unmet need for treatment in adult patients with type II or III SMA regardless of ambulatory status. The limitations of the real-world evidence (RWE) available to CDEC prevented the committee from concluding that nusinersen would fill the unmet needs expressed by patients and clinicians.

- Patient and clinician groups described cases of patients appearing to benefit from treatment with nusinersen. However, based on the presented evidence, CDEC was unable to determine that the magnitude of the treatment effect in the RWE could be attributed to nusinersen. Due to the heterogeneity in the natural history and clinical presentation of SMA in adults CDEC was unable to identify the characteristics of the patients who might experience benefit. The clinical experts emphasized to CDEC that there is substantial heterogeneity in disease disability across patients with type II and III SMA regarding ambulation and other motor function abilities. The clinical experts also noted that the natural history of SMA has a variable manifestation of functional decline over time. It was also discussed that trained physical activity alone can improve patients' physical function.
- The clinical experts discussed the potential to conduct an RCT in adult patients with SMA and considered that a properly conducted RCT would be feasible despite SMA being a rare disease. The committee discussed that based on the available observational evidence, the benefit of nusinersen in this population was uncertain, and would benefit from more conclusive evidence, especially given the potential risks associated with the administration of nusinersen. CDEC also discussed that RWE would generally not be adequately robust to replace RCT evidence, particularly in determining treatment effects but may support clinical trial data and fill in gaps about clinical application where long-term RCTs are not possible.
- CDEC noted that the National Institute for Health and Care Excellence (NICE) RWE Framework advises that data relevance is key, specifically related to provision of sufficient information to produce robust and relevant results; it also highlights that the RWE must be of sufficient duration to be relevant in a particular disease state. In the studies CDEC considered for type II and III SMA in adults, the RWE outcomes were measured in months; for a disease that is lifelong, this suggests that the duration of the RWE is not sufficient to meet the criteria of relevance. The NICE framework further highlights that the amount, reason, and handling of missing data in RWE is an important consideration. CDEC considered that the RWE for nusinersen had large amounts of missing data, and that the results suggested that the data may not be missing at random but possibly due to lack of efficacy.
- CDEC discussed the lack of pathobiological plausibility in the mechanism of action of nusinersen in adult patients with SMA, as the loss of motor units has been established in all SMA types in early age.
- CDEC discussed the risk-benefit profile of using nusinersen in adult patients, considering the uncertainty in the clinical effectiveness of nusinersen in providing disease stabilization or motor function improvements, accompanied by the harms and potential risks of pain, bleeding, infection, and nerve damage associated with the intrathecal route of administration in the spines of more complex adult patients. Stakeholder feedback received by CADTH highlighted that side effects or negative aspects of nusinersen were related to the method of drug administration, which was described as invasive and requiring multiple visits and/or travel.
- The sponsor submitted a systematic review and meta-analysis of patients with type II and III SMA by Coratti et al. CDEC discussed that there was considerable heterogeneity in the studies, given the inclusion of both ambulant and non-ambulant type II and type III SMA patients, as well as the inclusion of both adult and pediatric patients. Additionally, the included studies had small sample sizes, limiting the conclusions that can be drawn from individual studies. Moreover, given the nature of the included studies, and the limitations

defined for the studies included in both the systematic review conducted by CADTH and the meta-analysis, the observed effects cannot be directly attributed to nusinersen. In their request for reconsideration, the sponsor submitted a secondary analysis, which was used in the EMA submission. This secondary analysis included the same primary studies as the Coratti et al. meta-analysis and the results therefore had the same limitations.

Background

SMA is a severe neuromuscular disease, characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness. The most common form of SMA, 5q SMA, makes up more than 95% of all cases and is an autosomal recessive disorder caused by homozygous deletion, or deletion and mutation, of the alleles of the survival motor neuron 1 gene (SMN1). A second set of the survival motor neuron gene, SMN2, acts in a similar capacity to SMN1 but is usually not sufficient on its own to maintain motor neurons. The number of SMN2 genes usually determines the severity of SMA.

SMA is a rare disease and estimates of its incidence and prevalence vary between studies. Currently, the incidence of SMA in Canada is unknown, though it is estimated that SMA is reported in 1 in every 6,000 to 10,000 live births. A recent review reported estimates of 700 to 2,140 active cases of SMA in Canada, with approximately 35 new cases per year.

SMA presents in various ways, depending on age of onset. Adult onset SMA presents as mild proximal muscle weakness, and is more severe in the lower limbs than the upper limbs. SMA is divided into 4 clinical subtypes that vary in age of onset, highest motor milestone achieved, and prognosis. Of interest to this review are type II and type III SMA. In SMA type II, age of onset is 6 to 18 months and patients have delayed motor milestones, respiratory issues, and the possibility of a shortened life expectancy. Patients with type II SMA achieve the milestone of sitting unsupported, but never walk independently. Patients with type II SMA represent about 20% to 30% of SMA cases, and most patients with SMA type II have 3 copies of SMN2. Patients with SMA type III are those with onset from 18 months to 18 years of age. Type III SMA makes up about 10% to 20% of SMA cases. These patients are able to walk independently at some point in their lives and typically have a normal life expectancy.

Treatment options for 5q SMA available in Canada consist of disease-modifying therapies (nusinersen, risdiplam), which stimulate the production of SMN protein, and gene replacement therapy (onasemnogene abeparvovec), which is a 1-time IV infusion that replaces missing or faulty SMN1 genes.

Nusinersen has been approved by Health Canada for the treatment of 5q SMA. Nusinersen is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in SMN2 messenger RNA transcripts made, through binding to a specific site in the SMN2 pre-messenger RNA. This leads to the translation of the messenger RNA into functional full-length SMN protein. It is available as a 2.4 mg/mL solution administered via intrathecal injection by lumbar puncture, and the dosage recommended in the product monograph is 12 mg (5 mL) of nusinersen given in 4 loading doses, with the first 3 administered in 14-day intervals at day 0, day 14, and day 28, with the fourth loading dose approximately 30 days after the third loading dose (day 63). Following the fourth loading dose, a maintenance dose should be administered once every 4 months.

Submission History

The original CADTH review of nusinersen conducted in 2017 included 1 randomized, double-blind, sham-controlled, phase III clinical trial (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 2 copies of the SMN2 gene. Nusinersen was recommended for reimbursement of patients with 5q SMA with 2 copies of the SMN2 gene, and in those whose disease duration was 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.

In 2019, nusinersen was reviewed as a resubmission, which included 15 unique studies: 3 RCTs (ENDEAR [N = 121], CHERISH [N = 126], and EMBRACE [N = 27]), 4 phase I uncontrolled trials along with their extension studies (CS1 [N = 28], CS2 [N = 34], CS10 [N = 18], and CS12 [N = 47]), 2 phase II uncontrolled trials (CS3A [N = 21] and NURTURE [N = 25]), 1 extension study that included participants from all trials except EMBRACE and NURTURE (SHINE [N = 207]), 2 observational studies, and 3 case series observational studies that outlined the experience with expanded access programs in several countries for patients diagnosed with SMA. In the resubmission, a conditional positive recommendation was granted for patients with 5q SMA with 2 or 3 copies of the SMN2 gene and with disease duration of less than 6 months, symptom onset after the first week after birth, and aged 7 months or younger; or those aged 12 years or younger with symptom onset after 6 months of age, and who never achieved the ability to walk independently.

As part of the reassessment for nusinersen, the sponsor is requesting that the reimbursement criteria for nusinersen be expanded to include adult patients (> 18 years of age) with type II and type III SMA regardless of ambulatory status.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of the 4 observational clinical studies in adult patients with type II or III SMA
- patients' perspectives gathered by patient groups: Cure SMA Canada (CSMAC), Muscular Dystrophy Canada (MDC), and the Love for Lewiston Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise in diagnosing and treating patients with SMA
- input from 1 clinician group; the Neuromuscular Disease Network for Canada (NMD4C)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- feedback on initial recommendation from stakeholders and reconsideration material provided by the sponsor.

Stakeholder Perspectives

Patient Input

Patient input for the CADTH reassessment of nusinersen was received from 3 groups: CSMAC, MDC, and the Love for Lewiston Foundation — all of which are registered charities.

Respondents to the surveys and interviews from CSMAC and MDC noted that as they approached adulthood, they experienced a decline in their physical abilities, highlighting that they have lost the ability to, or are just barely able to, walk as adults. Along with the loss of gross motor skills, patients noted a significant impact on activities of daily living due to a progressive loss of life skills and overall independence, losing the ability to dress themselves, feed themselves, swallow, or turn over in bed, and transferring for the purpose of toileting. Additionally, patients experience a lack of energy and lose the strength in their voice, making communication difficult, which impacts their ability to meet the requirements to maintain employment. They also experience an increase in hospitalizations and need for supportive equipment. The devastation of disease progression and loss of function with a disease with full mental capacity has a severe negative impact on mental health and well-being. Patient groups noted that, coupled with the continued inability to access effective treatments, there is a significant increase in anxiety, depression, and self-harm among patients, requiring additional mental health support. Lastly, with the loss of physical function, patients require alterations to their homes for accessibility, which has a considerable financial impact.

Patient and caregiver responders identified an unmet need for access to treatments in the adult SMA population that offer stability and improved quality of life (QoL) through greater independence, improved strength (primarily in the arms and in respiratory function), and halting of progression. Patients believe, with improvements in these facets, they can achieve greater independence and better QoL. Patients also noted that some of the largest barriers to treatment, and challenges with currently available treatment, are the unreasonable costs, the mode of delivery with intrathecal therapy, and the potential harms of treatment.

Patients described their experience with treatments that included nusinersen, risdiplam, and alternative management of the disease. Many patients spoke about not having experience with any disease-modifying treatment owing to lack of access to therapies. In the CSMAC survey, 41 patients (47%) provided information about their experience with SMA treatments; 32 (78%) of whom were receiving nusinersen, and 9 (22%) of whom were receiving risdiplam. Many of the patients from the CSMAC and MDC surveys and interviews were treatment naïve as a result of limited access to SMA treatments in Canada. Of the patients receiving nusinersen, 79% reported that they experienced improved respiratory function, endurance, upper limb and core strength, and voice, with 15% reporting stabilization of their disease. The remaining 6% reported no stabilization or improvement. Patients were receiving treatment with nusinersen for 1 to 3.5 years. Negative experiences reported by patients receiving treatment with nusinersen included experiencing a wearing-off of treatment and a drop in function shortly before the next maintenance dose, which was subsequently rectified after treatment. Additional negative experiences included temporary headaches, discomfort from intrathecal injections, and the need to travel and/or miss work to receive treatment. Regardless, patients felt that the benefits of nusinersen, including gains in function, improved strength and energy, and disease stabilization, far outweighed the negative aspects of receiving this treatment. Several patients from the MDC interviews revealed that they switched to risdiplam after the initiation of nusinersen due to limited access, financial

constraints, and difficulties with the intrathecal administration. In the absence of or in addition to pharmacological therapies, patients also described using alternative ways to manage their SMA, such as physiotherapy, exercise, and traditional Chinese medicine.

Clinician Input

Input From Clinical Experts Consulted by CADTH

In adult patients with type II and III SMA, the clinical expert panel identified an unmet need for treatments that can change the natural course of the disease, including the ability to reverse the weakness associated with motor neuron degeneration, as there are currently no disease-modifying treatments available for adults. Experts agree that the goals of treatment are dependent on the type of SMA, given the high degree of heterogeneity in the disease and disability, and agree that treatment should be individualized based on the specific manifestations of the disease.

Currently, the mainstays of disease-modifying treatment for treatment-naïve adults with type II and III SMA are non-pharmacologic treatments, such as occupational therapy, physiotherapy, and speech-language pathology — which are aimed at supporting function, mobility, and independence — as well as supportive measures including ventilation, nutritional assistance, and assistive devices. If nusinersen is recommended in treatment-naïve adults with type II and III SMA, the clinical expert panel noted that it could be considered as a first-line treatment. It was also noted that risdiplam has recently been given a positive CDEC recommendation in younger adults; thus, the treatment paradigm may shift in the future. As noted by 1 expert, nusinersen has received funding in Quebec for the treatment of adult patients with type II and type III SMA and is currently being used in this population. Regardless, the clinical experts suggested that for the adult, treatment-naïve population, there is no evidence to guide whether other medications should be tried before nusinersen.

The experts highlighted the lack of higher-level evidence (i.e., from randomized controlled trials [RCTs]) in this population to determine which adult patients with SMA are most likely to respond to treatment with nusinersen. The experts hypothesized that patients with higher functioning and who are ambulatory may demonstrate better responses because they have more nerves, leading to better function. In addition, the clinical experts believed that patients without complex spines are more likely to have a better risk-benefit profile. However, most of the experts stressed that the earlier treatment is administered (i.e., in pre-symptomatic children), the greater the benefit observed, although there was some disagreement among the panel members as to considering age a factor when determining response. Conversely, the clinical expert panel noted that patients least suitable for treatment with nusinersen are those with complex spines due to spinal fusion surgery, those who cannot tolerate lumbar punctures, and those who have previously been treated as infants or children, as there is no evidence for these patients.

Clinically, there are numerous outcomes and measures to determine response to treatment. The clinical experts agreed that — given the variation in response to treatment and individualized treatment goals — several outcome measures are used to determine the benefits of treatment, including motor function outcomes and respiratory outcomes, as well as other outcomes such as bulbar function, strengthening of speech, or functional independence. The experts noted that in patients with type II and III SMA, disease progression occurs slowly over the course of years; thus, the impact of treatment on these outcome measures is not likely to be seen over a short period of time.

The clinical expert panel agreed that the main reasons for discontinuation would be progression or worsening of disease, as well as any major complications or adverse events (AEs) from therapy. One clinical expert noted that, based on experience with nusinersen in the adult population, the most common reason for discontinuation is patient desire to stop, citing lack of improvement and inability to tolerate the treatment. The panel agreed that all patients with SMA should be receiving care at a tertiary centre with a variety of neuromuscular specialists and a multidisciplinary team, with access to interventional radiology or neurosurgery and the ability to admit patients due to potential procedural or treatment-related complications.

Clinician Group Input

CADTH received the Clinician Group Input from the Neuromuscular Disease Network for Canada (NMD4C), a pan-Canadian network launched in 2020 bringing together clinical, scientific, technical, and patient expertise in neuromuscular disease with the aim of improving the care, research, and treatment of neuromuscular diseases for all Canadians. A total of 8 clinicians with experience treating SMA patients provided input for this submission.

The clinician group highlighted the 3 main disease-modifying treatments for SMA, including nusinersen, risdiplam, and onasemnogene abeparvovec. The clinician group agreed that treatment goals for later onset SMA would be to maintain current level of motor function and strength; achieve disease stabilization, including avoiding the need for ventilation; promote independence; and improve overall HRQoL. The clinician group highlighted that risdiplam may be the only other treatment option for these patients. In this case, they noted that either nusinersen or risdiplam could be tried first. The clinician group expressed that younger patients are most likely to derive benefit from nusinersen, and noted that it may be difficult to accurately identify adult patients who are most likely to derive benefit from nusinersen. The clinician group stated that clinically meaningful response to treatment in adults is likely to consist of stabilization of motor and respiratory function, maintenance of independence, and fewer hospitalizations. Moreover, they noted that maintaining the ability to speak and avoiding a need for ventilatory support have profound impacts on patient QoL, autonomy, and the ability to maintain vocational and social roles. The clinician group emphasized that the current provincial monitoring requirements are too frequent and there is significant variability between provinces. They agreed that patients should be assessed at treatment initiation, at 6 months, and then annually afterwards, to reduce the patient burden and strain on health care resources, given the slowly progressive functional decline over a matter of years. Lastly, the clinician group noted that nusinersen must be administered by or under the direction of health care providers who are experienced in performing lumbar punctures at designated treatment centres.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for nusinersen:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy

- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Description of Studies

As part of the reassessment for nusinersen, the sponsor provided CADTH with 5 observational studies, 1 open-label extension study, and 1 critical review and meta-analysis. A total of 4 studies were included in the report, and the critical review and meta-analysis was summarized in the Other Relevant Evidence section. While the other 2 studies were described in the report, they were not further discussed because they were considered outside the scope of this review.

The study by Hagenacker et al. (n = 124) was a German prospective, multi-centre, non-comparative observational study evaluating the safety and effectiveness of nusinersen in adult patients with 5q SMA. The study by Maggi et al. (n = 116) was an Italian retrospective, non-comparative cohort study evaluating the safety and effectiveness of nusinersen in patients with type II and type III SMA. The EU Registry Study (n = 252) was an observational, registry-based cohort study using combined data evaluating the safety and effectiveness of nusinersen in adults with 5q SMA from 3 prospective and retrospective European registries (SMArtCARE, CuidAME, and the International SMA Registry [ISMAR]) in 2 subcohorts: a before-after treatment with nusinersen group of patients with predominantly type III SMA (n = 74) or type IV SMA (n = 1), and a comparative dataset from a total of 252 adults with type III SMA (235 patients who had been treated with nusinersen and 17 who had not). The study by Pera et al. (n = 144) was an Italian observational, non-comparative, registry-based study from ISMAR of ambulant and non-ambulant type III SMA patients treated with nusinersen.

All studies included treatment-naïve adults with SMA. Across studies, most patients had type III SMA (62% to 100%), mainly with 3 or 4 copies of SMN2. Type II SMA was infrequently reported, with only 45 and 13 patients with type II in the Hagenacker et al. and Maggi et al. studies, respectively. No patients with type II SMA were included in the EU Registry Study or the study by Pera et al. Across studies, 37% to 56% of patients were considered ambulatory. Baseline motor function scores were high, with mean HFMSE scores at baseline ranging from 20.74 to 30.75, mean RULM scores at baseline ranging from 20.87 to 27.57, and mean 6-minute walk test (6MWT) distance at baseline ranging from 300.87 m to 323.03 m.

Effectiveness Results

HFMSE

In the Hagenacker et al. study, the mean change from baseline in HFMSE scores was 1.73 points (95% CI, 1.05 to 2.41) at 6 months (N = 124), 2.58 points (95% CI,1.76 to 3.39) at 10 months (N = 92), and 3.12 points (95% CI, 2.06 to 4.19) at 14 months (N = 57). The proportion of patients who had an increase of 3 points in HFMSE score were 28%, 35%, and 40% at 6 months, 10 months, and 14 months, respectively. In the Maggi et al. study, the mean change

from baseline in HFMSE scores was 1.48 points (SD = 2.28), 2.44 points (SD = 2.8), and 2.85 points (SD = 2.93) at 6 months (N = 103), 10 months (N = 75), and 14 months (N = 46), respectively, for all type III SMA patients. In all SMA patients at 6, 10, and 14 months, increases of 3 or more points in HFMSE score occurred in 28%, 38%, and 49% of patients, respectively. In the EU Registry Study, the slope for the change in HFMSE score per week was −0.00006 points per week (95% CI, −0.00955 to 0.009428) before treatment with nusinersen, and 0.2575 points per week (95% CI, 0.01038 to 0.04112) following treatment with nusinersen (N = 75). In the analysis comparing patients treated with nusinersen to untreated patients, the slope for the change in HFMSE score was 0.02907 points per week (95% CI, 0.01930 to 0.03884) in patients treated with nusinersen (N = 235) compared to −0.01129 points per week (95% CI, −0.03289 to 0.01031) in untreated patients (N = 17). In the study by Pera et al., at 12 months, the mean change from baseline in HFMSE was 0.79 points (95% CI, −0.29 to 1.87; N = 45), with the HFMSE results showing decline in 11.1% of patients, remaining stable in 53.3% of patients, and improving in 35.6% of patients.

RULM

In the Hagenacker et al. study, the mean change from baseline in RULM scores was 0.66 points (95% CI, 0.26 to 1.05) at 6 months (N = 120), 0.59 points (95% CI, 0.15 to 1.03) at 10 months (N = 90), and 1.09 points (95% CI, 0.62 to 1.55) at 14 months (N = 58). An increase in RULM score of 2 points or more was observed in 28 (23%) patients at 6 months, while 74 (64%) showed no meaningful change, and 28 (23%) declined. In the Maggi et al. study, the mean change from baseline in RULM score was 0.31 points (SD = 1.97), 0.61 points (SD = 2.08), and 0.86 points (SD = 2.18) at 6 months (N = 102), 10 months (N = 71), and 14 months (N = 44), respectively, for all type III SMA patients. Patients with type II SMA had a greater change in mean RULM scores than those with type III SMA, with scores of 0.8 points (SD = 1.95) at 6 months (N = 12), 1.67 points (SD = 1.8) at 10 months (N = 9), and 1.6 points (SD = 1.52) at 14 months (N = 5). A 2-point change in RULM score in all SMA patients at 6, 10, and 14 months was shown in 21%, 28%, and 35% of patients, respectively. In the EU Registry Study, the slope for the change in RULM score per week was −0.00745 points per week (95% CI, −0.01401 to 0.0009) before treatment with nusinersen, and was 0.002569 points per week (95% CI, −0.00533 to 0.01047) following treatment with nusinersen (N = 75). In the analysis comparing patients treated with nusinersen to untreated patients, the slope for the change in RULM score was 0.01168 points per week (95% CI, 0.004957 to 0.01841) in patients treated with nusinersen (N = 235) compared to 0.003936 points per week (95% CI, −0.01030 to 0.01817) in untreated patients (N = 17). In the study by Pera et al., at 12 months, the mean change from baseline in RULM was 0.07 points (95% CI, −0.48 to 0.63; N = 55), with the RULM results showing decline in 13.0% of patients, remaining stable in 75.9% of patients, and improving in 15.6% of patients.

6MWT

In the Hagenacker et al. study, the mean change from baseline in 6MWT score was 22.12 m (95% CI, 8.7 to 35.6) at 6 months (N = 47), 31.14 m (95% CI, 15.2 to 47.1) at 10 months (N = 37), and 45.96 m (95% CI, 25.4 to 66.6) at 14 months (N = 25). In the Maggi et al. study, change from baseline in 6MWT score was only available for type III SMA walkers, demonstrating a mean change in 6MWT score of 14.66 m (SD = 27.57) at 6 months (N = 48), 26.45 m (SD = 34.6) at 10 months (N = 35), and 23.11 m (SD = 51.2) at 14 months (N = 24). The proportion of patients achieving a minimum 30-metre improvement in 6MWT score was 29% at 6 months, 46% at 10 months, and 42% at 14 months. In the EU Registry Study, the slope for the change in 6MWT score per week was −0.03399 m (95% CI, −0.4373 to 0.3694) following treatment with nusinersen (N = 75). In the analysis comparing patients treated

with nusinersen to untreated patients, the slope for the change in 6MWT score per week was 0.2633 m (95% CI, 0.09922 to 0.4274) in patients treated with nusinersen (N = 235) compared to −0.7148 m (95% CI, −1.2789 to −0.1506) in untreated patients (N = 17). Mean change from baseline in 6MWT score for adult patients in the Pera et al. study at 12 months was 0.52 m (95% CI, −19.85 to 20.89; N = 17).

Other Effectiveness Outcomes

Respiratory outcomes of forced vital capacity (FVC)/forced expiratory volume in 1 second (FEV1) were only evaluated in the Maggi et al. study, with mean changes in percent-predicted FVC from baseline for all SMA type III patients at 14 months of 6.47% (SD = 9.22). Mean change in percent-predicted FVC at 14 months was not available in patients with type II SMA due to sample size constraints. The mean change from baseline at 14 months in percent-predicted FEV1 was 5.86% (SD = 9.22) for all type III SMA patients at 14 months. Mean change in percent-predicted FEV1 at 14 months was not available for type II SMA patients.

Other outcomes of interest to this review including bulbar function, survival, hospitalization, HRQoL, anatomic-related outcomes, and caregiver burden were not assessed in the included studies.

Harms Results

Harms were infrequently reported in the included studies, with all but 1 study (Pera et al.) reporting the frequency of harms. When reported, the frequency of AEs in the included studies ranged from 30% to 41.4%, and they were considered mild to moderate by the investigators. The frequency of serious AEs was low in all studies when reported.

In the Hagenacker et al. study, 2 patients withdrew from the treatment at 10 months because of adverse drug reactions. In the Maggi et al. study, nusinersen treatment was stopped in 2 type III SMA patients (1.7%) after 6 months due to lack of subjective benefit and poor tolerability of repeated lumbar puncture. Withdrawals due to AEs were not reported in the EU Registry Study, or the study by Pera et al.

The most frequently reported notable harms of interest to this review were lumbar puncture-related AEs; however, these were not reported in the EU Registry Study or the study by Pera et al. Post-procedural complications of headache (35% and 37.1%), and back pain (22% and 8.6%) were the most frequently reported AEs in the Hagenacker et al. and Maggi et al. studies, respectively. The frequency of headache and back pain was not reported in the study by Pera et al., but they were noted as the most frequently occurring AEs. Other notable harms, including serious infections, renal toxicities, and coagulation abnormalities, were infrequently reported in the included studies.

No deaths were noted in any of the studies.

Critical Appraisal

No RCTs focusing on treatment-naïve adult patients with type II or III SMA were identified as part of the CADTH literature search, and all available and included studies were of observational design, focusing on real-world data, which have more limitations than RCTs.

The studies included in this reassessment are associated with lower internal validity due to the limitations in design, enrolled patient populations, and statistical analysis. The

included studies shared a common limitation pertaining to the study design: they were non-comparative and thus the results observed cannot be attributed to the treatment with nusinersen. However, the EU Registry Study included an untreated comparison group, albeit with a sample size of 17 patients (see details below). The studies included in this reassessment also suffer from a high level of selection bias, reporting bias, and information bias. In all studies, selection criteria were limited to patients with SMA who were able to complete at least 6 months of treatment with nusinersen, selecting for patients who were able to complete the induction dosing, as well as selecting for those who were able to tolerate and/or could receive doses. Moreover, included patients were mostly those with type III SMA, with seemingly higher functional status at baseline, according to ambulatory status and baseline motor scale scores. No (or limited) techniques were used to adjust for potential selection biases across studies. In all studies, important potential confounders and treatment effect modifiers that were not identified or considered, which may influence the results, include training for the outcomes of interest, routine exercise, and close observation; other routine care such as physiotherapy and occupational therapy; and the placebo effect. The extent to which uncontrolled confounders and treatment effect modifiers influenced the results is unclear. In all studies, no protocol was identified, and it was not possible to determine whether sample sizes (ranging from 67 to 252 patients) were appropriate for the research question and objectives of each study. The EU Registry Study conducted analyses on 2 groups: 1 of 235 patients treated with nusinersen compared to 17 untreated patients, and 1 pre- and post-treatment analysis consisting of 75 patients. Due to the limited population in the untreated group, the results observed could not be attributed to treatment with nusinersen. The proportion of patients lost to follow-up was infrequently reported in the included studies, though there was a notable proportion of patients with a lack of longer-term follow-up at 14 months compared to earlier times of assessment. With the exception of the EU Registry Study, no imputation of missing data was conducted, with missing data impacting the validity of the results.

As previously mentioned, selection bias in the included populations was noted as key limitation. Patients enrolled in the included studies consisted mainly of those with type III SMA (62% to 100%), with few patients with type II SMA (11.2% to 36%), which was noted by the clinical experts to be higher than what they see in clinical practice. The patients included in the 4 studies were considered higher-functioning patients with SMA, based on the high prevalence of type III disease, with most patients having 3 or 4 copies of SMN2, and proportion of ambulatory patients (37% to 56.03%). Moreover, baseline motor function scores were considered high, suggesting a population with less severe disease. As such, the included study populations were unrepresentative of the reimbursement request (lack of patients with type II SMA), and the results may not be generalizable to adult patients with type II and III SMA in Canada. Given that up to half of all patients across studies were non-ambulatory, it was discussed with the clinical experts that the HFMSE and 6MWT might not be appropriate outcome measures in all patients, which further limits the evaluable population and the generalizability of the results. HRQoL and other patient-reported outcomes, which were outcomes important to patients, were not assessed in the included studies, and therefore the effect of nusinersen with respect to these outcomes remains unknown. The maximum follow-up time across studies was 14 months, which was considered insufficient to assess clinically meaningful change in outcomes in adult patients with type II or III SMA, due to the slowly progressing nature of the disease, as well as natural history.

Indirect Comparisons

No indirect evidence was included in the sponsor's submission to CADTH or identified in the literature search that matched the inclusion and exclusion criteria of this review.

Other Relevant Evidence

Other Sponsor-Submitted Evidence

As part of the reassessment for nusinersen, the sponsor submitted a publicly available critical review and meta-analysis of patients with type II and III SMA. The objective of the meta-analysis by Coratti et al. was to critically review the literature reporting real-world data on motor function in patients with type II and III SMA treated with nusinersen to establish possible patterns of efficacy by subdividing the results according to SMA type, age (pediatric versus adults) and type of assessment. Only results related to the adult population with type II or III SMA were of interest to this reassessment.

The meta-analysis was informed by a systematic review of existing literature. A total of 14,627 articles were identified. Following study selection, 19 papers reporting data on efficacy in patients treated with nusinersen and untreated patients, using structured assessments in type II and III SMA, were selected. Pooled analyses were conducted at multiple levels: first a rough evaluation on the overall benefit of treatment versus no treatment was run, including the largest available evidence, even if heterogeneous. The effect size was estimated using random-effect models and heterogeneity among studies was quantified by the I^2 coefficient. Meta-regression analysis was undertaken to identify possible sources of heterogeneity among studies. Motor function outcomes included HFMSE, RULM, 6MWT, Medical Research Council (MRC) scale for muscle strength, and Children's Hospital of Philadelphia — Adult Test of Neuromuscular Disorders (CHOP-ATEND). Meta-regression was not conducted for the MRC and CHOP-ATEND outcomes and they are not summarized. Meta-regression analyses were employed with a random-effects model using aggregate-level data. Only studies with complete data available (sample N, mean, SD or 95% CI) were included in the meta-analysis.

Pooled mean changes in HFMSE score, RULM score, and 6MWT from baseline in the adult population from the meta-regression analysis were 1.87 points (95% CI, 1.05 to 2.68), 0.64 points (95% CI, 0.27 to 1.01), and 20.28 m (95% CI, 1.17 to 39.40), respectively.

The meta-analysis was based on an adequately conducted and reproducible systematic literature search. It was unclear if the inclusion and exclusion criteria for population, outcomes, and study design were pre-specified. A quality assessment of the included studies was conducted using the RoBANS tool. No interpretation on the quality of studies was conducted; however, as all studies were observational, most studies were noted to suffer from a high level of bias in selection of participants. All publicly available studies summarized in the review conducted by CADTH (Hagenacker et al., Maggi et al., and Pera et al.) were included in the submitted meta-analysis. Outcomes included in the meta-analysis were appropriate and relevant to the Canadian context, with HFMSE, RULM, and 6MWT most commonly included in studies, though there were differences in reporting and time of assessment. Most of the included studies had a follow-up time ranging from 10 to 14 months, which was noted by the clinical experts consulted by CADTH to be insufficient to observe clinically meaningful changes in motor function of adult patients. There was considerable heterogeneity in the studies, given the inclusion of both ambulant and non-ambulant patients with type II and type III SMA, as well as the inclusion of both adult and pediatric patients. Additionally, the included studies had small sample sizes, limiting the conclusions that can be drawn from individual

studies. Overall, there was a moderate to considerable level of heterogeneity in the included studies across outcomes, with I^2 values ranging from 43% to 71%. Pooled estimates of mean change for motor function outcomes favoured nusinersen treatment in the adult population; however, the pooled estimates generally displayed wide 95% CIs, particularly for the 6MWT, and in many cases crossed the zero-meridian, indicating a high level of variability in these cohorts and substantial imprecision in estimates of treatment effect. Additionally, the change from baseline in motor function outcomes was minor, and in discussion with the clinical experts, there is uncertainty in what constitutes a clinically meaningful change in the adult population for these outcome measures. Moreover, given the nature of the included studies, and the limitations defined for the studies included in both the systematic review conducted by CADTH and the meta-analysis, the observed effects cannot be attributed to nusinersen.

Evidence Identified From the Literature

A mix of 8 non-comparative, observational studies were identified in the literature search that met all inclusion criteria of the systematic review with the exception of study design, as they consisted of descriptive observational studies. As with the studies provided by the sponsor, the effectiveness of nusinersen in these studies is highly uncertain due to the non-comparative study design, selection bias, and relatively small sample sizes of adults with type II and III SMA.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Adult patients with SMA
Treatment	Nusinersen in combination with real-world care (RWC) (respiratory, nutritional, and orthopedic care for type II and III SMA)
Submitted price	Nusinersen, 2.4 mg/mL: $118,000 per 5 mL vial
Treatment cost	The cost for nusinersen is $708,000 in the first year of treatment and $354,000 in subsequent years
Comparators	RWC alone Risdiplam in combination with RWC was considered in a scenario analysis
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (60 years)
Key data source	• Clinical efficacy for patients receiving nusinersen was modelled using evidence from Hagenacker et al. • Natural history for patients receiving RWC alone was modelled using evidence from Kaufmann et al.

Component	Description
Key limitations	• The available clinical studies were primarily non-comparative in nature and could not provide any conclusive evidence in support of a clinical benefit with nusinersen in comparison with RWC alone or risdiplam in the short term with regard to motor function milestones, HRQoL, or any other outcomes that are important to patients, nor was there any long-term data available in the target population of adults with SMA type II or III who have not received prior treatment. • The submitted model based on motor function milestones does not capture all key aspects of SMA in adult patients (e.g., loss of functional status, bulbar status, and requirement of nutritional support) expected to affect their HRQoL. • The submitted model has technical limitations and produces results that lack face validity (i.e., cannot produce equal QALYs when attempting to assume equal efficacy for nusinersen in comparison with RWC alone), which introduces uncertainty into the sponsor's estimates of cost-effectiveness. • The impact of treatment-related AEs and the mode of treatment administration on patient quality of life were not captured in the sponsor's model. Clinician and patient input indicate that complications and additional harms related to intrathecal injections are of concern. • Minor limitations also identified included the exclusion of risdiplam from the base-case analysis and the inclusion of caregiver utilities that overestimate the incremental benefit associated with nusinersen.
CADTH reanalysis results	• Given the key limitations with the available clinical evidence, no conclusions can be drawn regarding the comparative clinical effects of nusinersen compared with RWC alone or risdiplam in adult patients with SMA type II or III. In addition. given the issues related to the model structure and programming that could not be addressed, CADTH could not derive a base case. • Assuming equal efficacy for nusinersen compared with RWC alone or risdiplam, nusinersen is associated with greater drug acquisition costs. However, this assumption does not account for treatment-related AEs, including those related to the intrathecal mode of administration, which could result in reduced quality of life (QALYs) for those on nusinersen. • Based on the available clinical information, there is no evidence available to suggest the costs of nusinersen should be higher than the costs for risdiplam, with a greater price reduction likely necessary to offset the costs associated with intrathecal administration and its complications. In comparison with RWC alone, a price reduction of at least 100% would be necessary for nusinersen to be considered cost-effective.

Budget Impact

CADTH identified key limitations with the sponsor's analysis related to the underestimation of market shares for nusinersen, uncertainty with the prevalence of type II and type III SMA in Canada, and lack of clarity surrounding discontinuation criteria for nusinersen. CADTH reanalysis increased the market shares for nusinersen. In the CADTH base case, the anticipated budget impact for reimbursing nusinersen for the treatment of adult patients with SMA type II and III is $23,240,632 in year 1, $44,044,233 in year 2, and $65,387,990 in year 3, for a 3-year total of $132,672,855. This estimate was substantially different from that of the sponsor. Uncertainty remains in this estimate due to the true prevalence rate of type II and type III SMA in Canada being unknown, as well as the availability of risdiplam.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Initial meeting date: April 27, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None

Reconsideration meeting date: July 28, 2022

Regrets: Three expert committee members did not attend

Conflicts of interest: None