CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Nusinersen (Spinraza)

Indication: Adult type II & type III SMA patients older than 18 years of age regardless of ambulatory status.

Sponsor: Biogen Canada Inc.

Recommendation: Do Not Reimburse

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Single Technology

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nusinersen not be reimbursed for the treatment of type II & type III spinal muscular atrophy (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., 2020, Maggi et al., 2020, EU Registry Study, and Pera et al., 2021). Although the studies generally suggested that treatment with nusinersen had a positive effect on motor function (measured by the HFMSE, RULM, and 6MWT), key limitations including the uncontrolled nature of the studies and a high degree of selection bias, resulted in a patient population that was not considered representative of adult patients with SMA in Canada. 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 one of temporal variability and substantial heterogeneity in the degree of disability and motor function. 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 an unmet need for disease modifying treatment options in adults with type II and type III SMA. 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 provides any clinically meaningful benefits in adults with type II or III SMA, regardless of ambulatory status.

Discussion Points

- 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.
- 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 and improvement and over time. It was also discussed that routine physical activity alone can have a profound effect on patients' physical function.
- 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 and 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 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 unclear, and would benefit from more conclusive evidence, especially given the potential risks associated with the administration of nusinersen.
- The sponsor submitted a review and meta-analysis of patients with type II and III SMA. 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.

Background

Spinal muscular atrophy (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 (SMN) 1 gene (SMN1). A second set of 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.

Spinal muscular atrophy 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 6,000-10,000 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.

Spinal muscular atrophy presents in various ways, depending on age of onset. Adult onset SMA presents as mild proximal muscle weakness, and more severe in the lower limbs than in the upper limbs. Spinal muscular atrophy is divided into four 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 six to 18 months and patients have delayed motor milestones, respiratory issues, and the possibly 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 three 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 one-time intravenous (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 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 two 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 who's 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 have had disease duration of less than 6 months, and symptom onset after the first week after birth and on or before 7 months of age or are 12 years of age or younger with symptom onset after 6 months of age, and 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 & 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

Stakeholder Perspectives

Patient Input

Patient input for the CADTH reassessment of nusinersen was received from 3 groups; Cure SMA Canada (CSMAC), Muscular Dystrophy Canada (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 and 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 wellbeing. 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 QoL through greater independence, improved strength (primarily in the arms and 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 to not having experience with any disease modifying treatment owing to lack of access to therapies. In the CSMAC survey, 41 (47%) patients provided information about their experience with SMA treatments; 32 (78%) of which were receiving nusinersen, and 9 (22%) 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 strengths 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, and discomfort from intrathecal injections, as well as the required travel and time off work to receive treatment. Regardless, patients felt that the benefit of nusinersen including gains in function, improved strength and energy, and disease stabilization far outweighs 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 in 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 agreed that treatment should be individualized based on the specific manifestations of the disease.

Currently, the mainstay of treatment for disease-modifying, 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 also recently been given a positive CDEC recommendation in younger adults, thus the treatment paradigm may shift in the future. As noted by one 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 prior to 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. As well, 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, though 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 the 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 center 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 eight clinicians with experience treating SMA patients provided input to this submission.

The clinician group highlighted the three 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 the avoidance of need for ventilation, to promote independence, and improve overall health-related quality of life (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 ability to speak and avoiding 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 healthcare providers experienced in performing lumbar punctures at designated treatment centers.

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 two 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., 2020 (n = 124) was a prospective, German, multicenter, non-comparative observational study evaluating the safety and effectiveness of nusinersen in adult patients with 5q SMA. The study by Maggi et al., 2020 (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., 2021 (n = 144) was an observational, non-comparative, registry-based study from ISMAR in Italy 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%), with mainly 3 or 4 copies of SMN2. Type II SMA was infrequently reported with only 45 and 13 type II patients in Hagenacker et al., 2020 and Maggi et al., 2020, respectively. No type II patients were included in the EU registry study or the study by Pera et al., 2021. Across studies, 37% to 56% of patients who were considered ambulatory. Baseline motor function scores were high, with mean Hammersmith Functional Motor Scale Expanded (HFMSE) scores at baseline ranging from 20.74 to 30.75, mean Revised Upper Limb Module (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 meters to 323.03 meters.

Effectiveness Results

Hammersmith Functional Motor Scale Expanded (HFMSE)

In Hagenacker et al., 2020, 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 Maggi et al., 2020, 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, 0.009428) prior to treatment with nusinersen, and was 0.2575 points per week (95% CI: 0.01038 −0.04112) following treatment with nusinersen (N = 75). In the analysis comparing nusinersen-treated patients to untreated patients, the slope for the change in HFMSE score was 0.02907 points per week (95% CI: 0.01930 – 0.03884) in nusinersen-treated patients (N = 235) compared to −0.01129 points per week (95% CI: −0.03289 −0.01031) in untreated patients (N = 17). In the study by Pera et al., 2021, at 12-months, the mean change from baseline in HFMSE was 0.79 points (95% CI: -0.29, 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 according to the authors.

Revised Upper Limb Module (RULM)

In Hagenacker et al., 2020, the mean change from baseline in RULM scores was 0.66 points (95% CI: 0.26–1.05) at 6 months (N = 120), 0.59 points (95% CI: 0.15–1.03) at 10 months (N = 90), and 1.09 points (95% CI: 0.62–1.55) at 14 months (N = 58). A greater than or equal to 2 points increase in RULM score were observed in 28 (23%) patients at 6-months, while 74 (64%) showed no meaningful change, and 28 (23%) declining. In Maggi et al., 2020, the mean change from baseline in RULM scores 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 numerically greater change in mean RULM scores than those with type III 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, 0.0009) prior to treatment with nusinersen, and was 0.002569 points per week (95% CI: −0.00533, 0.01047) following treatment with nusinersen (N = 75). In the analysis comparing nusinersen-treated patients to untreated patients, the slope for the change in RULM score was 0.01168 points per week (95% CI: 0.004957, 0.01841) in nusinersen-treated patients (N = 235) compared to 0.003936 points per week (95% CI: −0.01030, 0.01817) in untreated patients (N = 17). In the study by Pera et al., 2021, at 12-months, the mean change from baseline in RULM was 0.07 points (95% CI: -0.48, 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.

6-Minute Walk Test (6MWT)

In Hagenacker et al., 2020, the mean change from baseline in 6MWT was 22.12 meters (95% CI: 8.7-35.6) at 6 months (N = 47), 31.14 meters (95% CI: 15.2-47.1) at 10 months (N = 37), and 45.96 meters (95% CI: 25.4-66.6) at 14 months (N = 25). In Maggi et al., 2020, change from baseline in 6MWT was only available for type III SMA walkers, demonstrating a mean change in 6MWT of 14.66 meters (SD: 27.57) at 6-months (N = 48), 26.45 meters (SD: 34.6) at 10-months (N = 35), and 23.11 meters (SD: 51.2) at 14-months (N = 24). The proportion of patients achieving a minimum 30-meter improvement in 6MWT 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 per week was -0.03399 meters per week (95% CI: -0.4373, 0.3694) following treatment with nusinersen (N = 75). In the analysis comparing nusinersen-treated patients to untreated patients, the slope for the change in 6MWT score per week was 0.2633 meters per week (95% CI: 0.09922, 0.4274) in nusinersen-treated patients (N = 235) compared to -0.7148 meters per week (95% CI: -1.2789, -0.1506) in untreated patients (N = 17). Mean change from baseline in 6MWT for adult patients in Pera et al., 2021 at 12-months was 0.52 meters (95% CI: –19.85–20.89; N = 17).

Other Effectiveness Outcomes

Respiratory outcomes of forced vital capacity (FVC)/forced expiratory volume in 1 second (FEV1) were only evaluated in Maggi et al., 2020, 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, anatomical-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 one study (Pera et al., 2021) reporting the frequency of harms. When reported, the frequency of AEs in the included studies ranged from 30% to 41.4% and were considered mild to moderate by the investigators. The frequency of serious adverse events (SAEs) was low in all studies when reported.

In Hagenacker et al., 2020, 2 patients withdrew from the treatment at 10-months because of adverse drug reactions. In Maggi et al., 2020, nusinersen treatment was stopped in 2 (1.7%) type III SMA patients after 6-months due to lack of subjective benefit and poor tolerability of repeated lumbar puncture. Withdrawals due to AEs (WDAEs) were not reported in the EU Registry Study, or the study by Pera et al., 2021.

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., 2021. 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., 2020, and Maggi et al., 2020 studies, respectively. The frequency of headache and backpain were not reported in the study by Pera et al., 2021, but were noted as the most frequently occurring AEs. Frequency of 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, type II or III SMA patients 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 those 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 type III SMA of 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, as well as the placebo effect, and the extent to which uncontrolled confounders and treatment effect modifiers factors 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 two groups: one of 235 nusinersen-treated patients compared to 17 untreated patients, and one pre- and post-treatment analysis consisting of 75 patients. Due to the limited population in the untreated group, the results observed were unable to 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 of mainly type III SMA (62% to 100%), with few type II patients (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 SMA patients 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 type II SMA patients), 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 may not be appropriate outcome measures in all patients, which further limits the evaluable population and the generalizability of the results. Health-related quality of life 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., 2021 was to critically review the literature reporting real-world data on motor function in type II and III patients treated with nusinersen to establish possible patterns of efficacy by subdividing the results according to SMA type, age (pediatric vs. 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 nusinersen-treated 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 vs. 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 in order 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 are not summarized. Meta-regression analyses were employed with 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: 1.05–2.68), 0.64 points (95% CI: 0.27–1.01), and 20.28 meters (95% CI 1.17–39.40), 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., 2020, Maggi et al., 2020, and Pera et al., 2021) 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 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. 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% CI's, 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

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., 2020. • Natural history for patients receiving RWC alone was modelled using evidence from Kaufmann et al., 2012.
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 regards to motor function milestones, health-related quality of life, 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 health-related quality of life. • The submitted model has technical limitations and produces results which 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 adverse events and the mode of treatment administration on patient quality 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

Component	Description
	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 adverse events, 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 three-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.

Canadian Drug Expert Committee (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.

Meeting Date: April 27, 2022

Regrets

One expert committee member did not attend

Conflicts of Interest

None