CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Risdiplam (Evrysdi)

Indication: For the treatment of spinal muscular atrophy (SMA) in patients 2 months and older.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: May 2021
Report Length: 12 Pages

Single Technology

RISDIPLAM (EVRYSDI — HOFFMANN-LA ROCHE LTD.)

Therapeutic Area: Spinal Muscular Atrophy

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that risdiplam should be reimbursed for the treatment of spinal muscular atrophy (SMA) in patients 2 months and older only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, single-arm study, FIREFISH Part 2 (N = 41), enrolled infants with SMA who were aged 2 to 7 months with symptoms onset before 3 months. Patients were required to have two copies of the SMN2 gene and not receiving permanent ventilation. FIREFISH Part 2 achieved the primary outcome in that 29.3% of infants were able to sit without support after 12 months on treatment, which was compared with a natural history threshold of 5% (P < 0.0001). The study also demonstrated improvements on motor and developmental milestones based on comparisons with pre-specified performance thresholds using the CHOP-INTEND and the HINE Section 2 scales. Additionally, 85.4% of patients receiving risdiplam, as compared with a pre-defined threshold of 42% (P < 0.0001), were alive and did not require permanent ventilation at month 12.

One phase III, double-blind, placebo-controlled study, SUNFISH Part 2 (N = 180), enrolled non-ambulatory patients with SMA aged 2 to 25 years of age. Most of the enrolled patients had three SMN2 gene copies (89.2% in risdiplam, 83.3% in placebo). At baseline, 10.8% were able to stand in the risdiplam arm and 10.0% in the placebo arm. SUNFISH Part 2 achieved its primary endpoint where patients who received risdiplam had an improvement in motor function with a mean difference versus placebo of 1.55 points (95%CI 0.30 to 2.81, P = 0.0156) in the change from baseline to month 12 in the Motor Function Measure 32 (MFM32) score. Overall, 38.3% of patients in the risdiplam arm were considered responders on the MFM32 (change of 3 points or more from baseline) compared with 23.7% in the placebo group (odds ratio 2.35; 95%CI 1.01 to 5.44, P = 0.0469). Patients who received risdiplam also had statistically significantly improved upper limb mobility versus placebo based on the change in RULM score (a mean difference versus placebo of 1.59 points [95%CI 0.55 to 2.62, P = 0.0028]).

CADTH reanalysis of the sponsor-submitted cost-utility model estimated that incremental cost-effectiveness ratio (ICER) of risdiplam compared with best supportive care (BSC) to be $1,203,108 per quality-adjusted life year (QALY) in patients with SMA type 1, and $37,378,163 per QALY in patients with SMA type 2 or 3. Risdiplam was less costly than nusinersen and the sponsor assumed equivalent efficacy between treatments. However, the lack of long-term comparative efficacy evidence means that incremental effectiveness, and thus cost-effectiveness, of risdiplam compared with nusinersen is highly uncertain.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Genetic documentation of 5q SMA homozygous gene deletion or compound heterozygote.	Consistent with diagnostic criteria for SMA used in main trials, FIREFISH Part 2 and SUNFISH Part 2.
2. Patients who are symptomatic and either: 2.1. Aged between 2 months and 7 months (inclusive), have a body weight greater than the third percentile, and genetic documentation of 2 copies of the SMN2 gene. **OR** 2.2. Aged 7 months and up to 25 years who are non-ambulatory and have genetic documentation of 2 or 3 copies of the SMN2 gene.	FIREFISH Part 2 demonstrated meaningful clinical benefit in motor function in patients with the characteristics described in 2.1. SUNFISH Part 2 demonstrated a benefit in motor function in patients aged 2 to 25 years. The benefit is likely to be clinically meaningful for some patients, although it is not possible to identify these patients prior to initiation of therapy with risdiplam. FIREFISH Part 2 included only children up to age 210 days (7 months), and SUNFISH Part 2 only included patients aged 2 to 25 years. Despite the lack of evidence in patients with SMA who have symptom onset between 7 months and 2 years of age, CDEC concluded that this limitation in the design of the studies should not exclude these patients from the reimbursement population for risdiplam.
3. Patient is not currently requiring permanent invasive ventilation.	There is no evidence to suggest a benefit in patients who reach an advanced state of SMA where permanent ventilation is required.
4. The maximum duration of initial authorization is 12 months.	Assessment of benefit from treatment with risdiplam occurred at 12 months in both trials. Authorization of funding for 12 months provides flexibility to accommodate the practical challenges of assessing clinical response after treatment initiation given the natural history of SMA.
Discontinuation	
1. Reimbursement of treatment with risdiplam should be discontinued when: 1.1. there is no demonstrated achievement in, or maintenance of, motor milestone function (as assessed using an age-appropriate measurement) after treatment initiation in patients aged between 2 months and 2 years at the time of treatment initiation; or 1.2. there is no demonstrated maintenance of motor function (as assessed using an age-appropriate measurement) after treatment initiation in patients who were aged between 2 years and 25 years at the time of treatment initiation; or 1.3. if permanent invasive ventilation is required.	Results from FIREFISH Part 2 and SUNFISH Part 2 indicated that only some patients will respond to therapy.

Reimbursement Condition	Reason
2. The decision to discontinue reimbursement should be based on two assessments separated by no longer than a 12-week interval, each done within six weeks of the annual renewal date.	This provides flexibility to accommodate the practical challenges of assessing clinical response to treatment given the natural history of SMA and variation in individual patient performance on functional tests used to assess response.
Prescribing	
1. Patient must be under the care of a specialist with experience in the diagnosis and management of SMA.	The diagnosis and treatment of SMA requires specialist medical care.
2. Risdiplam should not be used in combination with nusinersen or onasemnogene abeparvovec.	There is no evidence to support combination therapy.
Pricing	
1. A reduction in price.	The economic evidence for SMA Type 1 patients suggests that risdiplam should be priced similarly to nusinersen. A price reduction of 99% for SMA Type 2 and 3 patients still resulted in very high ICER estimates in comparison with BSC.

BSC = best supportive care; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2.

Implementation Guidance

1. CDEC heard from clinical experts that functional testing may demonstrate considerable variation between different visits. As such, evaluation for determining discontinuation should be based on the best performance over at least two assessments, separated by no longer than 12-week interval and excluding intercurrent illnesses.
2. The definition of non-ambulatory in the SUNFISH Part 2 study was the inability to walk unassisted (i.e., without braces, assisted devices such as canes, crutches or calipers, or person or hand-held assistance) for 10 m or more at the time of enrollment.
3. Permanent ventilation was defined in the included studies as the need for a tracheostomy or requirement of 16 hours or more of non-invasive ventilation (e.g., BiPAP) per day or intubation for more than 21 consecutive days in the absence of, or following the resolution of, an acute reversible event.
4. Given the extraordinarily high cost of risdiplam, the budget impact of using risdiplam will be considerable, even if the price is reduced substantially. Therefore, the reimbursement conditions reflect the importance to CDEC of identifying those patients with SMA who are most likely to benefit from treatment. CDEC noted that risdiplam was expected to reduce budget impact among SMA type 1 patients, but greatly increase the overall drug budget among the full indicated population.
5. Sequencing of risdiplam relative to other medications indicated for the treatment of SMA is an important evidence gap. CDEC noted that children who have been receiving medications indicated for SMA — such as nusinersen, which has a difficult and invasive mode of administration that haspotential for related adverse events — and who meet the initiation conditions above should not be precluded from receiving reimbursement of treatment with risdiplam.
6. Functional assessment tools for patients with symptom onset before 2 years of age could include the Hammersmith Infant Neurological Examination (HINE) Section 2. The clinical experts recommended the HINE Section 2 for assessment of infants.
7. Functional assessment tools for patients 2 years and older could include the Hammersmith Functional Motor Scale Expanded (HFMSE). Patients who cannot be assessed by the HFMSE should have their assessment conducted by another appropriate tool. The clinical experts recommended the HFMSE and revised upper limb module (RULM) scales for non-ambulatory older patients who are not infants.

Discussion Points

- SMA is a rare, genetic, life-threatening, and seriously debilitating neuromuscular disorder that has a heavy burden on patients, caregivers, society, and the health care system. Nusinersen and onasemnogene abeparvovec are currently the only other approved drug treatments for patients with SMA. Despite the availability of these two agents, CDEC heard patient and clinical

expert input that there remains a need for additional safe and effective treatments for SMA. CDEC noted patient and clinician concerns regarding the potential for harm when administering nusinersen intrathecally every three months and uncertainty that the intended dose consistently reaches the site of action, which could lead to progressive bulbar muscle weakness in some patients. CDEC discussed that the different route of administration between risdiplam and nusinersen may inform patient preference and the practicality of prescription. CDEC also noted that onasemnogene abeparvovec is not indicated in patients who may have later onset SMA or have high titer of antibodies to the adeno-associated virus (AAV) capsid vector.

- CDEC discussed the challenge of recommending reimbursement criteria for risdiplam on the basis of SMA subtype (i.e., SMA type I, II, III, or IV) considering that there is overlap between SMA subtypes on some criteria, and that the achievement of major motor milestones such as sitting or walking independently is both a goal of treatment and a criterion used for classifying patients. In addition, with the availability of disease modifying therapies, these classifications are likely to become obsolete as patients show symptoms consistent with one classification but achieve motor milestones that are consistent with a potentially better classification.

- CDEC identified numerous limitations associated with the single-arm trial design of the FIREFISH Part 2. Although CDEC considered the observed treatment effects of risdiplam on assessed outcomes in the study to be clinically meaningful, the lack of a concurrent control group precludes a precise estimation of the magnitude of benefit.

- CDEC identified several limitations associated with the double-blind, placebo-controlled trial of SUNFISH Part 2. Most important was that there were uncertainties whether the observed benefit of risdiplam was clinically meaningful and whether any efficacy is expected in adolescent and adult patients. CDEC noted that the magnitude of benefit with risdiplam in adolescent and adult patients, especially in patients aged 18 to 25 years, may be smaller than in younger patients.

- Unlike nusinersen and onasemnogene abeparvovec, risdiplam is currently not approved for use in patients younger than two months of age. This includes pre-symptomatic patients identified through newborn screening. CDEC noted that studies are undergoing for the effects of risdiplam in this subpopulation.

Background

Risdiplam has a Health Canada indication for the treatment of SMA in patients two months and older. The product monograph reports that there are limited data on risdiplam for patients over 25 years of age. Risdiplam is a SMN2 pre-mRNA splicing modifier. Risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript leading to an increased production in functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels. Risdiplam is available as a dry powder that must be reconstituted to an oral solution by a health care provider prior to being dispensed. Risdiplam is administered once daily after a meal at approximately the same time each day. The dosage of risdiplam is determined by age and weight as follows:

- 2 months to less than 2 years of age: 0.20 mg/kg
- 2 years or older and less than 20 kg of body weight: 0.25 mg/kg
- 2 years and older and 20 kg or more of body weight: 5 mg

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- A systematic review that included one single arm uncontrolled trial and one randomized controlled trial.
- Patients' perspectives gathered by patient groups, from Muscular Dystrophy Canada (MDC) and Cure SMA Canada (CSMAC).
- Input from six clinical specialists with expertise diagnosing and treating patients with SMA.
- Input from one clinician group, Neuromuscular Disease Network for Canada (NMD4C).
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Two patient input submissions for this review from Muscular Dystrophy Canada (MDC) and Cure SMA Canada (CSMAC).

The patient input submissions from MDC and CSMAC were based on semi-structured interviews, virtual interviews, a focus group of five adult patients and eight parent caregivers, and a survey of patients and caregivers that gathered 96 responses. All respondents lived in Canada and all data were collected between October and December 2020.

Six main themes were apparent, which have been listed in order of frequency reported: (1) an enormous impact on activities of daily living; (2) breathing, swallowing, and mobility are mostly affected; (3) significant dependence on caregiving supports; (4) loss of independence and control; (5) pain, age-related fatigue, and mental health; and (6) fear of falling.

Some of the major health concerns expressed by both patient groups included: respiratory function (and illnesses like pneumonia), muscle strength, fine motor skills, falls and safety, nutrition (inability or losing ability to chew and swallow), voice and speech, mental and emotional health, and being easily fatigued. Transportation time and distance along with accessibility when out in public were noted as important considerations in day to day life. The desire to maintain or regain independence for as long as possible was common among responses, despite the constant fear of progressive loss of function and declining health. Living with SMA requires a high degree of dependence on both caregivers and equipment, additional therapy, and medical appointments, all of which lead to exhaustion for both patients and caregivers as well as increased strain on mental health and relationships.

Many patients who contributed to the patient group input were receiving nusinersen. While positive about its therapeutic impact they described challenges with the treatment that included the intrathecal administration, the costs and disruption of travel, the possibility of hospitalization, and the side effects experienced after a lumbar puncture. Being aware of risdiplam, respondents felt that a daily, oral treatment would have a positive impact on their lives if it meant fewer hospital visits, less strain on hospital resources and staff, was convenient and easily accessible, and would allow patients and families to have stable careers, education, and family lives. Both patient groups also noted that access to new disease modifying therapies is variable across Canada and there are still many patients who would benefit from such therapies but do not yet have access to them.

Clinical Evidence

Clinical Trials

The systematic review included one single arm uncontrolled trial and one randomized controlled trial.

FIREFISH Part 2 (N = 41) is an ongoing, open-label, single-arm, phase III trial that investigated the efficacy and safety of risdiplam after 12 months of treatment in infants with 2 copies of the SMN2 gene (categorized by the investigators as having SMA type I), body weight greater than the 3rd percentile for age, and not receiving invasive ventilation. A total of 41 infants received risdiplam at an age-determined dose. These infants had an average age of 5.2 months (standard deviation [SD] 1.47), had onset of symptoms reported at a mean age of 1.64 months (SD 0.70), and a mean disease duration of 3.59 months (SD 1.35). At baseline, 4.9% of the infants were able to keep their head upright, while 85.4% did not demonstrate any motor milestone achievement, and 70.7% did not require any form of ventilatory support.

SUNFISH Part 2 (N = 180) is an ongoing, double-blind, placebo-controlled, phase III trial that investigated the efficacy and safety of risdiplam after 12 months of treatment in patients aged 2 to 25 years (inclusive) who were non-ambulatory. Patients were randomized (2:1 ratio) to risdiplam or placebo. The mean age of enrolled patients was 9.9 years (SD 5.8) in the risdiplam group and 10.3 years (SD 6.1) in the placebo group. Patients belonging to the age group of 18 to 25 years formed the smallest age group (11.7% in risdiplam, 13.3% in placebo), followed by the age group 12 to 17 years (25.0% in risdiplam, 26.7% in placebo). Most patients had 3 SMN2 gene copies (89.2% in risdiplam, 83.3% in placebo) and greater than two-thirds were diagnosed by investigators as having SMA Type 2 (70.0% in risdiplam, 73.3% in placebo). At baseline, 10.8% of patients in the risdiplam group and 10.0% in the placebo group were able to stand.

Key limitations of the FIREFISH Part 2 included:

- The absence of a concurrent control arm in the form of a placebo control or an active control. This increases the risk of overestimating the treatment effect for risdiplam in the single arm trial. Without a randomized comparison to a control group, natural fluctuations in the disease cannot be adjusted for, nor can the effects of known and unknown confounders.
- The patient population was highly selective. The study did not include children younger than 2 months of age, older than 6 months, or who had three copies of the SMN2 gene. Therefore, there is no data to directly inform on the extent of the effects of risdiplam for these patients.

Key limitations of the SUNFISH Part 2 included:

- While adult patients with SMA were included in the SUNFISH Part 2 trial, they represented the smallest age group in the study (a total of 12.2%). The design of the study, including the outcome measures and duration, was likely not the most appropriate to evaluate the effects of risdiplam in this age group of patients with SMA whose disease progression may be different from younger patients with SMA. Therefore, the generalizability of the overall results is lowest in the 18 to 25 year age group.
- SUNFISH Part 2 excluded ambulatory patients. Considering the nature of SMA, where alpha motor neurons are irreversibly lost as disease progresses, patients with higher motor function may have a greater number of alpha motor neurons than patients who have lost such motor functions. Ambulatory patients may thus exhibit a variation in the response compared to non-ambulatory patients, and the generalizability of the SUNFISH Part 2 results to this patient population is unclear.

Outcomes

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

- motor function related outcomes
- respiratory related outcomes
- survival
- health-related quality of life
- safety outcomes.

The primary outcome in FIREFISH Part 2 was achieving sitting for five seconds without support after 12 months of treatment as assessed by the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) tool. Other key secondary outcomes that were included in a statistical testing hierarchy were: proportion of patients who achieve a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at month 12, proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at month 12, proportion of motor milestone responders as assessed by the HINE Section 2 at month 12, proportion of patients alive without permanent ventilation at month 12, and proportion of patients sitting without support for 30 seconds (item 26 of BSID-III) at month 24. No minimum important difference (MID) was identified for the BSID-III total score or for the CHOP-INTEND total score, while the HINE Section 2 had an estimated MID of greater than 1 point.

The primary outcome in SUNFISH Part 2 was the change from baseline in the MFM32 score at month 12. Key secondary outcomes within the statistical testing hierarchy were: proportion of patients with a change from baseline MFM32 total score of 3 or more at month 12, change from baseline in the total score of the RULM at month 12, change from baseline in total score of the HFMSE at month 12, change from baseline in Forced Vital Capacity (FVC) at month 12, change from baseline in caregiver reported SMA Independence Scale (SMAIS) Total Score at month 12, and proportion of individuals rated as 'improved' on the clinician-reported global impression of change (CGI-C) at month 12. The sponsor proposed that 3 points or more difference on the MFM32 may indicate the acquisition of a new function or the improvement of several functions. The RULM has an estimated MID of 2.9 points, the HFMSE has an estimated MID of more than 2 points, and the SMAIS has an estimated MID of 1 to 5 points. No MIDs were identified for the other outcomes.

Efficacy

In FIREFISH Part 2, 29.3% of infants were able to sit without support after 12 months on treatment. This was contrasted with a natural history threshold of 5% (P < 0.0001). Of the reported secondary outcomes that were within the statistical testing hierarchy (at 12 months of treatment), 56.1% of infants had a CHOP-INTEND score of 40 or higher (P < 0.0001 against a performance criterion of 17%), 90.2% achieved an increase of at least 4 points in the CHOP-INTEND score from baseline (P < 0.0001 against a performance criterion of 17%), and 78.0% (32 / 41) were considered motor milestone responders assessed through the HINE Section 2 (P < 0.0001 against a performance criterion of 12%). At month 12, 85.4% of patients were alive and did not require permanent ventilation, which was statistically significant compared with a pre-defined natural history threshold of 42% (P < 0.0001).

More function improved in patients who received risdiplam in SUNFISH Part 2 with a mean difference versus placebo of 1.55 points (95% CI 0.30 to 2.81, P = 0.0156) for the change from baseline on the MFM32 score. The first secondary outcome tested within the statistical testing hierarchy after the primary outcome was the MFM32 responders (change of 3 points or more from baseline). This outcome showed that 38.3% of patients in the risdiplam group were considered responders, compared with 23.7% in the placebo group (odds ratio of 2.35; 95% CI 1.01 to 5.44, P = 0.0469). Subsequently, the change in the RULM score was tested, with a mean difference versus placebo of 1.59 points (95% CI 0.55 to 2.62, P = 0.0028) in favour of risdiplam. The next two co-outcomes were tested, the change from baseline in the total score of HFMSE and the change from baseline in best percentage predicted value FVC, failed to achieve statistical significance. Patient and clinician-reported outcomes, measured through the SMAIS and CGI-C tools, were next on the statistical testing hierarchy, but since the previous outcomes failed to achieve statistical significance, no additional statistical testing could be performed based on the pre-specified analysis plan.

Harms (Safety)

In FIREFISH Part 2, at least one adverse event was reported in all enrolled infants. Upper respiratory tract infection was the most commonly reported adverse event (46.3%), followed by pneumonia (39.0%), pyrexia (39.0%) and constipation (19.5%). Serious adverse events were reported in 58.5% of the infants (24 / 41), with most of the serious adverse events related to respiratory problems or respiratory infections. Three infants died during the study; two deaths were attributed to pneumonia, and one to respiratory failure.

In SUNFISH Part 2, at least one adverse event was reported in 92.5% and 91.7% of enrolled patients in the risdiplam and placebo arms, respectively. Upper respiratory tract infection was the most commonly reported adverse event (31.7% in risdiplam, 30.0% in placebo), followed by nasopharyngitis (25.8% in risdiplam arm, 25.0% in the placebo arm), pyrexia (20.8% in risdiplam arm, 16.7% in placebo arm), and headache (20.0% in risdiplam arm, 16.7% in placebo arm). Serious adverse events were reported in 20.0% of patients who received risdiplam and 18.3% in patients who received placebo. Most of the serious adverse events were related to respiratory problems or respiratory infections.

Indirect Evidence

One sponsor-submitted indirect treatment comparison (ITC) was reviewed. The ITC compared risdiplam to nusinersen in two distinct patient populations, infantile onset SMA (classified as SMA Type 1) and later onset SMA (classified as SMA Type 2 or 3). An unanchored matched-adjusted indirect comparison (MAIC) was performed for the SMA Type 1 population and included the FIREFISH study for risdiplam (pooled subgroup of PART 1 with Part 2) and the ENDEAR study for nusinersen. The results of the SMA Type 1 unanchored MAIC suggest a hazard ratio for ventilation free survival of risdiplam versus nusinersen of 0.20 (95%CI 0.06 to 0.42) and an overall survival hazard ratio of 0.26 (95%CI 0.03 to 0.66). Motor function assessment using the HINE Section 2 showed favourable results for risdiplam in the outcomes of motor milestone response, full head control, and sitting without support while the outcome of rolling was favourable in the direction of nusinersen. Two outcomes, sitting with and without support and standing, did not show a clear direction. However, limitations such as poor statistical robustness in the data for many of the comparisons and low likelihood that the assumption that all known and unknown effect modifiers and prognostic factors were accounted for within the model was met, among other important limitations, means there is considerable uncertainty regarding the actual observed effect that is attributed to risdiplam.

An anchored MAIC was used for later onset SMA and included the SUNFISH study for risdiplam and the CHERISH study for nusinersen, with the placebo arm in SUNFISH and the sham arm in CHERISH acting as a common comparator. Due to large discrepancies in the inclusion and exclusion criteria between the studies, the ITC only used a subset of patients from the SUNFISH part 2 study that would have been included in the CHERISH study, reducing the sample size of SUNFISH part 2 by 62% and breaking randomization in SUNFISH part 2. The sample sizes were further reduced to make the populations more homogeneous; the resulting effective sample size was too small to provide a robust analysis, as reflected by very wide confidence intervals. No concrete conclusions could be drawn from the results of this analysis.

Economic Evidence

Cost and Cost-Effectiveness

At a cost of $193.9725 per mg, the daily cost for patients 2 years of age and older (and 20 kg and over) is $970, for a total annual cost of $354,000. The average daily cost and annual cost for patients who are between 2 months and 2 years of age are $256 and $93,456, respectively.

The sponsor submitted a cost-utility analysis assessing risdiplam compared to nusinersen, and BSC defined as care provided in the absence of disease-modifying treatment, for the treatment of SMA. The sponsor submitted two models to address this target population. One model was for patients with SMA type 1, often referred to as infantile-onset SMA. The second model was for patients with SMA type 2 or 3, where onset typically occurs after 18 months and further into childhood or adolescence. Two models were considered to better reflect the different natural history, age of onset, baseline motor function and treatment efficacy between these two populations. Both model structures were based on motor function milestone achievement. The submitted models reported both quality-adjusted life-years (QALYs) and life-years (LYs) over a lifetime time horizon of 25 years in the SMA type 1 population and 80 years in the SMA type 2 or 3 population. The base case analyses were conducted from the perspective of the Canadian public health care payer

In SMA type 1, FIREFISH informed treatment efficacy with risdiplam, while ENDEAR informed an unanchored matching-adjusted indirect comparison for risdiplam with BSC. For the SMA type 2 or 3 population, SUNFISH informed transitions between motor function health states for risdiplam and BSC. In both subgroups, the sponsor assumed equivalent treatment efficacy (motor function milestones, overall survival and event-free survival) between risdiplam and nusinersen.

CADTH identified the following key limitations with the sponsor's submission:

- In the absence of direct comparative information, the magnitude of clinical benefit, with regards to motor milestone achievement and survival (i.e., mortality and requirement of permanent ventilation) with risdiplam compared with BSC or nusinersen is highly uncertain. Further, the lack of long-term comparative efficacy of risdiplam or nusinersen adds to the extent of clinical uncertainty. It is not clear if they are equally effective.
- The sponsor's base cases included health state utilities for two informal caregivers per patient in addition to patient health state utilities. CADTH acknowledges that caregiver burden is significant with SMA, though this does not align with CADTH requirements for drug submissions. The inclusion of non-patient utility overestimated the total QALY benefits observed with risdiplam.
- The submitted model structures and associated assumptions may not appropriately capture all key changes in patient quality of life, including SMA-related developments such as the requirement of nutritional support or loss in functional status.
- The sponsor's model assumed that mortality was independent from illness severity, with identical mortality rates for all patients. This assumption is not appropriate, as patients would have different mortality based on their motor, respiratory and bulbar function. This contributed meaningful uncertainty to the results.

In a reanalysis, CADTH removed caregiver utilities. CADTH could not address the remaining key limitations, including limitations with the submitted model structure and the comparative efficacy of risdiplam with nusinersen and BSC. Interpretations of the estimated mean ICER and price reduction should take the resulting uncertainty into account.

Compared with BSC, risdiplam is associated with an ICER of over $1.2 million per QALY in SMA type 1 and an ICER over $37 million in SMA type 2 or 3. Risdiplam is not considered cost-effective at a conventional willingness to pay threshold. Price reductions of 99% would not be sufficient to reach a $50,000 per QALY threshold in either subgroup. Given the assumption of equivalent treatment efficacy, risdiplam continued to dominate nusinersen in reanalysis due to the drug acquisition costs associated with risdiplam being less than the publicly available price of nusinersen.

Budget Impact

The sponsor estimated that the three-year budget impact of risdiplam would be $77,420,166. CADTH noted that the sponsor's analysis underestimated the proportion of patients with SMA type 1 currently receiving treatment, underestimated the likely rate of treatment retention for risdiplam, and made assumptions about the proportion of patients covered under public plans that may not reflect reality. After accounting for these limitations, CADTH estimated a three-year budget impact of $87,744,812 ($30,183,701 in year 1, $29,146,849 in year 2, and $28,414,263 in year 3). CADTH noted that risdiplam was expected to decrease budget among patients with SMA type 1 (i.e., risdiplam cost saving), but that this reduction was outweighed by the additional cost among patients with SMA type 2 and 3.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 21, 2021 Meeting

Regrets

One committee member did not attend.

Conflicts of Interest

None

CADTH

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