A.40	Risdiplam – spinal muscular atrophy – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: The body of evidence suggests that risdiplam may have a beneficial effect in children and adults with SMA, that outweigh clinical undesirable effects, such as harms, high costs, and other burdens of treatment. Furthermore, there is a considerable need for options of treatments that provide an increase in health-related quality of life and better function in a disease with a bad prognosis.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Spinal muscular atrophy (SMA) is a hereditary genetic disease caused by a defect or mutation in the *SMN1* gene. The incidence of SMA vary from 1 in 6,000 to 1 in 12,000 live births. The data and research on the incidence of SMA is predominately from Europe and North America. The root cause is SMN protein deficiency (usually from SMN1 mutation). SMN protein is essential for motor neuron survival; deficiency weakens the muscles and leads to debilitation. A younger age at symptom onset and fewer SMN2 genes (which can express some SMN protein) increase the severity of the disease. SMA Type 1 is considered the most aggressive Type of SMA and is the leading genetic cause of death in early infancy. Access to risdiplam is particularly critical for later-stage SMA types. There are currently no SMA treatments included in the EML.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The body of evidence is not ideal due to the catastrophic clinical characteristics of the condition. Evidence from the FIREFISH Part 2, includes 41 patients with Type 1 SMA. The median age of onset of symptoms of Type 1 SMA was 1.5 months (range: 1.0-3.0 months). The median age at enrolment was 5.3 months (range: 2.2-6.9 months). At baseline, the median Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) score was 22.0 points (range: 8.0-37.0) and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0 (range: 0.0-5.0). At Month 24, 44% of patients achieved sitting without support for 30 seconds. Patients continued to achieve additional motor milestones as measured by the HINE-2: 80.5% were able to roll, and 27% of patients achieved a standing measure (12% supporting weight and 15% standing with support). Overall, untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age. SUNFISH Part 2 is the randomized, double-blinded, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized with a 2:1 ratio to receive either Evrysdi at the therapeutic dose or placebo. The primary endpoint was the motor function assessment (MFM-32). Patients had a mean baseline MFM-32 score of 46.1 and a Revised Upper Limb Module (RULM) score of 20.1. For primary analysis, the change from baseline in MFM-32 total score at Month 12, showed a clinically meaningful and statistically significant difference between patients treated with risdiplam and placebo. At the time of the 24-month analysis, the patients who were treated with risdiplam for 24 months overall experienced maintenance of improvement in motor function between month 12 and month 24.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The evidence from harms stems from the same trials for efficacy. The most common AE was fever, diarrhea, and a rash. These AE were reported in less than 10% of the patients that received risdiplam. AE that occurred in at least 5% of patients treated with risdiplam and at an incidence of ≥ 5% greater than on placebo related to fever (22% vs 17%), diarrhea (17% vs 8%), rash (17% vs 2%), mouth and aphthous ulcers (7% vs 0%), arthralgia (5% vs 0%), and urinary tract infection (5% vs 0%).
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Adverse events are common but are usually linked to the evolution of the clinical condition. Those linked to treatment and more frequent to placebo are usually considered manageable.

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Specialist care is needed for the use of risdiplam in patients with SMA of all types.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Most agencies approving agree that risdiplam might be cost-effective. The cost is around 340,000 USD per year per patient in the US, and 93,456 CAD in Canada. This is a cheaper option than other SMA options such as nusinersen (annual cost 708,000 CAD).
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: There might be a need for accelerated approval for some countries, but this should be on a case by case basis.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: