A.40	Risdiplam – spinal muscular atrophy – EML and EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: Rare diseases, as a group, constitute a relevant public health need – but individual rare conditions may not. This is said in respect to the relevance of priority diseases, not to the individual or societal perceived importance of specific conditions. The relevance in this case resides in the estimations that SMA may be a leading cause of death in early infancy. The number of studies that assess individual treatments are still very small in number and in sample size; trials are of short duration and samples may be biased. Possibly RWD generated form patient registries will provide RWE, as has been the case with other rare diseases. All three existing therapies are very costly and access in low, middle and even high-middle-income countries is bound to be nil or very low. Several important questions remain whether all SMA types are treatment-amenable; which of the existing therapies are superior, safe, cost-effective in different jurisdictions; the best moment to initiate treatment; what is the point in which no response from treatment will be had; if treatments can be combined or in a first-line, second- line sequence[1]. Drug approval is based on relatively weak short-term evidence, without any long-term data. Most evidence, albeit incipient, is for newborns/infants. Measuring outcomes and comparing data is especially difficult, with different motor scales. more biomarkers are needed[2]. In the published studies not all participants in any of the treatment groups responded to treatment, and all displayed significant mortality. The therapeutic area is in the middle of a paradigm shift regarding standard of care[1]. Despite novel SMN-dependent therapies, uncertainties regarding treatment response and long-term outcomes for patients with SMA remain. Achieving age-appropriate milestones and treating the effects of SMA on peripheral tissue as well as complementary approaches to tackling the whole motor unit are still in course[3]. None of the treatments offers a cure for symptomatic individuals because vanished neurons cannot be replaced[1]. So early diagnosis (and early effective treatment) is key – which may point to a future use only for pre-symptomatic individuals and neonates. However, the problems, extreme difficulties in access and costs associated with early diagnosis and screening (pre-symptomatic), lacking evidence for later-onset, make a very difficult argument in favor of supporting a recommendation for inclusion -at this time – to the WHO EMLc or to the EML.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Rare diseases, as a group, constitute a relevant public health need – but individual rare conditions may not. This is said in respect to the relevance of priority diseases, not to the individual or societal perceived importance of specific conditions. The relevance in this case resides in the estimations that SMA may be a leading cause of death in early infancy. Spinal muscular atrophy (SMA) is a genetic condition, inherited in an autosomal recessive pattern. It results from homozygous deletions of the survival motor neuron 1 (SMN1) on chromosome 5q13.2 in 92% of cases. The carrier frequency is 1/50, with an incidence of 1/12,000 for live births and population prevalence of 1/100,000[4]. It is estimated that it may be the leading cause of death in early infancy. SMA is described as various types and classified based on metrics of disease presentation, including the age of onset, highest motor function achieved, and age of death. Type 0 is the most severe and children usually do not survive past 12 months. Type 1 SMA (Werdnig Hoffman Disease), is the most common, occurring in months 0-6 of life with an average age of death of less than 24 months and accounts for approximately 50% of the cases of SMA. Types 2 and 3 (Kugelberg Welander Disease), are milder and diagnosed in early childhood with longer life expectancies depending on the individual disease severity. Type 4 SMA is adult-onset in the 2nd or 3rd decade of life and is the highest functioning form of the disease[4]. Transforming a fatal condition to a chronic one necessitates expanding relevant clinics and services and treatment provision for what Hjartarson and col. call “new survivors”[1].

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: There are very few studies, with small samples as can be expected with rare diseases. Quality of evidence in average is low. There are some narrative reviews and one SR published as full-free text[5] (but funded by manufacturer). No head-to-head clinical trials have directly compared the efficacy of these disease-modifying therapies (DMTs) in SMA[5]. Risdiplam is the only orally administered drug approved for the treatment of SMA. The genetic deficit is caused by deletions or other alterations in SMN1, which is often partially compensated for by another similar, but less effective gene, SMN2. Ridisplam functions as an SMN2 gene splicing modifier leading to higher levels of SMN protein. The mechanism of action of Risdiplam is designed to increase the survival of the SMN2 protein levels systemically by including exon 7 into SMN2 mRNA transcripts. The highest increase in SMN protein levels was seen in infants with SMN type 1[4]. Oral administration is a significant advantage because it reaches tissues involved in the multisystem pathogenesis of this disease. Ridisplam was FDA approved in 2020 for use in patients two months of age and older. After four weeks of treatment, Risdiplam lead to a greater than a 2-fold increase from baseline levels of SMN protein. Is has been observed that results were sustained for at least a year[4]. The advantage of risdiplam is that it penetrates the blood-brain barrier, increasing the level of SMN protein in both the central nervous system and peripheral organs. *Trials* FIREFISH (Phase II, III) – ongoing. enrolled 62 infants with SMA type 1, four of whom received a low dose (final dose at month 12 is 0.08 mg of risdiplam per kilogram body weight per day) and 17 received a high dose (final dose at month 12 is 0, 2 mg per kilogram per day). SUNFISH (Phase II, III) - included 231 patients with a later onset of symptoms. Risdiplam has been given to people between 2 and 25 years of age with type 2 or 3 SMA. JEWELFISH (Phase II) - was a multicenter, open-label study in a group of subjects (177) with a confirmed diagnosis of 5q-autosomal recessive SMA. Patients in the study were 6 months to 60 years of age and had previously received RG7800 (RO6885247), nusinersen, olesoxime, or Zolgensma. RAINBOWFISH (Phase II) – ongoing in 25 pre-symptomatic infants with genetically confirmed SMA from birth to 42 months of age. *Comparative effectiveness*[5] **(data on comparative effectiveness was funded by manufacturer)** The HR for Event-Free Survival of risdiplam versus nusinersen was estimated to be 0.20 (95% CI: 0.06–0.42) in the Matching-adjusted indirect comparisons (MAIC) analysis. Analyses also suggest risdiplam increases survival relative to best supportive care (BSC), with HR of 0.09 (95% CI: 0.02–0.19). MAIC results were also suggestive of increased Overall Survival with risdiplam relative to nusinersen (HR: 0.26 [95% CI: 0.03–0.67]) and BSC (HR: 0.10 [95% CI: 0.01–0.24]. No concrete conclusions on the relative efficacy in Event-Free Survival (EFS) between risdiplam and onasemnogene abeparvovec with Simulated Treatment Comparison (STC) (HR of 0.94 (95% CI: 0.03–4.06). The 14-month survival probability (one of the endpoints in STR1VE-US), was 91% for onasemnogene abeparvovec and 93% for risdiplam in the STC. No patient on BSC achieved a motor milestone response. A comparison of risdiplam with BSC gave an OR of 293.30 (95% CI: 184.94–532.02). (HINE-2) MAIC analysis of risdiplam *versus* nusinersen gave an OR of 3.97 (95% CI: 2.03–8.38). In regard to scales´ endpoints, risdiplam may be more effective than nusinersen and BSC in terms of an improvement in CHOP-INTEND scores. STC analyses did not provide sufficient evidence to draw concrete conclusions on the relative efficacy between risdiplam and onasemnogene abeparvovec with regard to the achievement of the following motor milestones: sitting without support ≥30 s (OR: 0.75 [95% CI: 0.15–5.26]), head control for ≥3 s (OR: 0.65 [95% CI: 0.07–5.38]), rolling back to sides (OR: 2.09 [95% CI: 0.42–13.73]) and standing with assistance (OR: 5.24 [95% CI: 0.35–1677.00]). Across both CHOP-INTEND endpoints, there was insufficient evidence to draw concrete conclusions on the relative efficacy between risdiplam and onasemnogene abeparvovec. Indirect comparisons support risdiplam as a superior alternative to nusinersen in Type 1 SMA[5].

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: Although data from SUNFISH, FIREFISH and JEWELFISH trials suggest that Risdiplam has a favorable safety profle[6], there are very few studies, with small samples as can be expected with rare diseases. Quality of evidence is low. There are some narrative reviews and one SR published as full-free text[5]. Systemic administration has benefits in terms of broader scope of organic tissues the drug can penetrate and modulate. However, AE profile may be compromised. Some noted effects In FIREFISH and SUNFISH trials are constipation, diarrhea, rash, fever, pneumonia, and vomiting. Others that are less common may include UTIs, arthralgias, and ulcers. There seems to be an effect of Risdiplam on reproductive organs and embryonal toxicity (contraceptive measures are recommended to female patients of reproductive age and potential effects on fertility should be discussed before treatment in males)[4]. Retinal toxicity was seen in studies with non-human primates but has not appeared in clinical studies. *In vitro* studies showed inhibition of certain biotransformation/elimination proteins (MATE1 and MATE2-K), which in turn may cause increased plasma levels of drugs that undergo the same pharmacokinetic pathway (eg, metformin)[1]. As to comparative safety, in the analysis of risdiplam against nusinersen, the OR was 0.38 (95% CI: 0.15–0.97) in the Matching-adjusted indirect comparisons (MAIC) analysis. *Versus* Best Supportive Care, the OR was 0.06 (95% CI: 0.01–0.23) for MAIC analysis. No concrete conclusions on relative safety in terms of the frequency of SAEs between treatments were found. The OR of risdiplam versus onasemnogene abeparvovec was 1.02 (95% CI: 0.22–5.08) in the STC[5]. **(data on comparative effectiveness was funded by manufacturer)**
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: The most common adverse reactions that occurred during clinical trials were fever, diarrhea, rash (10%), constipation, nausea, vomiting, headache, mouth ulcers and sores, joint pain or urinary tract infections. Especially in SMA infants, respiratory tract infections, pneumonia, bronchiolitis, hypotonia, constipation and vomiting have been observed[7]. Less common side effects of Risdiplam in later-onset SMA include mouth and aphthous ulcers, arthralgias, and urinary tract infections. The drug must be avoided in patients with any hepatic impairment. Because of risk of fetal harm in animal studies, is not recommended in pregnant women. Risdiplam was found to have adverse effects on reproductive organs[4].

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: *Administration* It is available as a powder for oral solution (60mg/bottle 0.75mg/ml when reconstituted with water), attaining 80ml total volume. The reconstituted solution is stable for 64 days under refrigeration. The dose depends on body weight, to a maximal dose of 5 mg in patients ≥2 years and ≥20 kg. Pharmacokinetics is dependent on age of the patient[4,7]. It is administered orally preferably after a meal and may be administered through a feeding tube. Dosage studies have been conducted in both healthy adults as well as SMA patients. Steady state is reached in 7–14 days[1]. The drug should be taken immediately after it is drawn into the oral syringe. Patients should drink water following administration of the drug. If not fully swallowed or if vomiting occurs, another dose is not recommended to make up for the lost dose[4]. Therapeutic regimen is once daily for 2 years followed by an open-label extension (OLE) phase of at least 3 years[7]. Treatment duration is still an open question for most SMA types. *Motor function scales*[8] Twelve different scales were found for patient assessment The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), The Hammersmith Infant Neurological Exam—Part 2 (HINE-2), The Motor Function Measure-20 (MFM-20), The Gross Motor Function Measure (GMFM), The Hammersmith Functional Motor Scale (HFMS), The Modified Hammersmith Functional Motor Scale (MHFMS), The Expanded Hammersmith Functional Motor Scale (HFMSE), The Revised Hammersmith Scale (RHS), The Revised Upper Limb Module (RULM), The 6-Minute Walk Test (6-MWT), Quantitative Muscle Testing (QMT), Neuromuscular Gross Motor Outcome (GRO). None are designed to assess everyday living functions, gross or fine motor functions, and none can be applied in all SMA individuals, including walkers, sitters, and non-sitters. Each scale rates patients in a different way, and it is not possible to translate the results from one scale to another. No scale includes the assessment of breathing and feeding (which have great impact on the quality of life) or subtle changes in severely affected patients. *Diagnosis and screening* For later onset SMA, clinical exams may reveal muscle weakness and hypotonia, motor difficulties, hyporeflexia, tongue fasciculations (involuntary twitches), among other signs. The standard tool for diagnosing SMA is molecular testing. This confirms 95% of suspected cases. SMN2 copy numbers are also determined to help predict the phenotypic severity of the disease, although the correlation is not absolute. If case is suspected and molecular testing is negative, an SMN1 dosage analysis and gene sequencing should be performed to analyze the possibility of a rarer genetic cause of the disease[4]. Screening recommendations include neurophysiologic studies (electromyography and nerve conductions), formal motor function assessments, and neurologic examination every 3-6 months until age two and every 6-12 months thereafter[9]. Understanding that early and pre-symptomatic treatment has great impact on outcomes, has led to the need for the implementation of newborn screening[9] using DNA extracted from dried blood spots with a PCR assay targeting SMN1 exon 7 which can be differentiated from SMN2 exon 7. SMA screening methods have high (100%) positive predictive value (day). The US implemented newborn screening programs for SMA, covering 74% of newborns. Screening all newborns in the United States for SMA would find about 364 annually, preventing approximately 100 children with SMA Type 1 from needing permanent ventilation and approximately 68 deaths each year[3]. Patients with SMA identified through the newborn screening program should have treatment available within 14 days of life. Prenatal cases identified because of carrier screening also allow for early treatment[2]. *Long-term follow-up* For successful long-term treatment of SMA, more knowledge of disease development is needed. SMN deficiency is embryonic, but even when therapy starts at pre-symptomatic stages, not all SMA patients respond equally well and symptoms progress[6]. In a first SR in 2022of long-term follow-up[10], no evidence on risdiplam that met the inclusion criteria could be identified in the systematic search. Long-term clinical data are lacking. There are uncertainties around disease stabilisation or improvement over time, persistence of gained abilities, and additional patient characteristics for clinical decision-making. Existing clinical data show that early treatment in SMA type 1 children seem have better outcomes. The evidence for later onset SMA types (SMA type 2 to type 4) is lacking[10]. Screening for, diagnosing, treating and following SMA patients can only be done by very specialized personnel. Direct and indirect needs and costs are considerable.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: This medicine faces huge affordability issues because of cost. Cost-effectiveness analyses are basically hard to produce since there are, yet no conclusive effectiveness analyses. There are technical opinions by the The Canadian Agency for Drugs and Technologies in Health (CADTH), by The National Institute for Health and Care Excellence (NICE), by Ireland's National Centre for Pharmacoeconomics (NCPE), by Zorginstituut Nederland who concluded for it being still not cost-effective in their high-income environments, despite acknowledging that there is unmet need and that perhaps, once additional evidence is produced it may perhaps be cost-saving, and patients may switch from other therapies. Nice recommended access through a managed access agreement. Paradoxically the drug was incorporated in Brazil, a high-middle-income country, for types I, II and III in Feb 2022[12]. The country has been overburdened with health litigation for access to medicines, and with a dispute with the manufacturer of Zolgensma, that withheld market availability due to pricing negotiations[11]. Cost of treatment for Type 1 a 25-yr horizon was BRL 3,227,472.67. ICER was calculated at BRL 5,150, 827.58/QALY. For types 2 and 3, for lifetime horizon cost of treatment was BRL 14,145,685.00. ICER was calculated at BRL 75,938,549.34[12,13]. (1 BRL = 0,1946 USD in 25 Feb 2023) The application expands on possibilities for lowering production costs, making the drug more affordable in the future, with generic versions. According to the applicant, production costs per kg would be 4,000 to 40,000 USD, depending on production scale. Prices of patent holder in high-income countries today range from $117 to $232 per milligram or $213,525 to $423,400 annually for a dose of 5 milligrams per day. The drug is on patent and there are currently no generic versions. The patent holder has filed numerous patents covering risdiplam since 2013, and the manufacturer has filed at least one patent in 22 national patent offices. And there are no existing or planned licensing agreements with generic manufacturers.
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: Risdiplam was approved in the US in 2020. Risdiplam is now market-approved in 81 countries and marketing authorization has been filed in a number of additional jurisdictions.
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: No WHO Guidelines available.

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