A.24 Risdiplam – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Two medications, nusinersen and risdiplam, and one gene therapy, onasemnogene abeparvovec, are the three main treatments for SMA. For many patients, the three SMA treatments are both highly costly and effective. However, many patients do not have access to onasemnogene abeparvovec or are ineligible because they are older than two. In LMIC contexts, where hospital access, resources, and infrastructure may be limited, onasemnogene abeparvovec, an AAV9 gene replacement therapy used to treat children under the age of two (or under 13.5 kg), must be handled and administered in a hospital setting with an appropriate containment level. Risdiplam is superior to the other medication in a number of ways for EML. Risdiplam is administered orally using an oral syringe once day after meals, but nusinersen needs an intrathecal injection every four months. Risdiplam can be administered at home and doesn't require hospitalization. Because it eliminates the need for specialized hospital visits and promotes greater accessibility for patients, this home-based administration paradigm is especially beneficial for LMICs. Patients receiving risdiplam in HIC are usually examined by their treating physicians for their regular standard-of-care examinations once every six months. Furthermore, there will probably be a less expensive generic version of risdiplam available soon. The cost of producing this medication is comparatively low. All that is needed for regulatory routes is evidence of bioequivalence. Patents for risdiplam have not been applied for or awarded in certain nations having GMP production capacity. I support the inclusion of Risdiplam and quality assured biosimilars on the EML and EMLc for the treatment of patients with spinal muscular atrophy.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? Major clinical trials, to date, for risdiplam include the SUNFISH trial in adults, the FIREFISH trial for infants, and the RAINBOWFISH trial. **FIREFISH:** In the infantile-onset SMA study (FIREFISH Part 2), an open-label trial with 41 participants, efficacy was established based on the ability to sit without support for at least five seconds. After 24 months of treatment, 38 infants were ongoing in the study and 18 infants (44% [90% CI 31–58]) were able to sit without support for at least 30 s ($p<0{\cdot}0001$ compared with the performance criterion derived from the natural history of untreated infants with type 1 spinal muscular atrophy). After 23 or more months of treatment, 81% of participants were alive without permanent ventilation. Although the study did not perform direct comparisons against children receiving a placebo (inactive treatment), these results compare favourably with the typical course of the untreated disease. Treatment with risdiplam over 24 months resulted in continual improvements in motor function and achievement of developmental motor milestones. **SUNFISH** The study of later-onset SMA was a randomised controlled trial that enrolled 180 participants, aged between 2 and 25 years, with less severe forms of the disease. 180 patients were randomly assigned to receive risdiplam (n=120) or placebo (n=60). Risdiplam resulted in a significant improvement in motor function compared with placebo in patients aged 2–25 years with type 2 or non-ambulant type 3 spinal muscular atrophy. Our exploratory subgroup analyses showed that motor function was generally	☒ Yes ☐ No ☐ Not applicable

improved in younger individuals and stabilised in older individuals, which requires confirmation in further studies. **RAINBOWFISH** RAINBOWFISH (NCT03779334) is an open-label, single-arm, multicenter, global clinical study enrolling infants aged from birth–6 weeks of age (at first dose), regardless of SMN2 copy number, without clinical signs of SMA at baseline. Infants will receive risdiplam for 24 months, followed by a 36-month extension. The primary endpoint of the study is the proportion of infants sitting without support for at least five seconds after month 12. RAINBOWFISH Preliminary efficacy and safety data: A total of 25 of the infants completed one year of treatment and 24 completed two years of treatment. **At month 12, 4 out of 5 (80%) of infants in the primary efficacy population (those with 2 SMN2 copies) could sit without support for at least five seconds. This significantly exceeds the expected performance of 5% based on the natural history of untreated Type 1 SMA.** **Secondary endpoints**: By month 12, 22 out of 23 (96%) of infants achieved motor milestones, including sitting without support. By year two, all infants with 2 SMN2 copies could sit unaided, and 3 of 5 (60%) could stand alone while 2 of 5 (40%) were able to walk independently. Infants with ≥3 SMN2 copies achieved 100% of the motor milestones, such as standing, sitting, and walking within the WHO windows of typical development. There are no direct head-to-head studies comparing risdiplam against the two other existing treatments for SMA.	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? **Comments:** In clinical trials, the most common adverse events included fever, diarrhea, rash, ulcers of the mouth area, joint pain (arthralgia) and urinary tract infections. Additional adverse events observed in the infantile-onset population included upper respiratory tract infection, pneumonia, constipation and vomiting. There are no deaths due to treatment and no adverse events that led to withdrawal or treatment discontinuation. **The majority of adverse events are not considered treatment related, but rather reflective of the age of the infants.**	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? These early results indicate **the value in early treatment with risdiplam before SMA symptoms appear. Patients with SMA have motor neuron degeneration before the onset of symptoms.** Once symptoms manifest, risdiplam cannot reverse them but can only help to prevent further progression. Early intervention with risdiplam, therefore, offers the best opportunity to counteract the effects of the disease, providing infants with pre-symptomatic SMA a significantly better chance of living with minimal disease progression and a better quality of life. More concretely, infants who received prophylactic risdiplam have the chance to live without the disabilities associated with SMA, an unparalleled advancement. Results from presymptomatic studies are particularly significant in nations without access to newborn SMA screening. In these situations, siblings of afflicted children who were diagnosed prenatally at birth or who were presymptomatic can receive treatment right	☒ Yes ☐ No ☐ Not applicable

away during the first few days of life. In nations with greater birth and consanguinity rates, where preimplantation genetic diagnosis is neither practical nor accessible, this is beneficial. Risdiplam (originator trade name Evrysdi) is currently sold as a powder for oral solution 60mg/bottle 0.75mg/ml when reconstituted. The total volume when reconstituted is 80ml. Each ml of constituted solution contains 0.75mg of risdiplam. The drug can be distributed in powder form, and subsequently constituted as an oral solution with water. Once mixed with water, the solution is stored in a refrigerator and can be used for 64 days. In addition to the existing oral solution, risdiplam is expected to be available in a new bioequivalent tablet form, pending FDA approval (anticipated early 2025). The single dispersible 5mg tablet offers several advantages, including a 2-year shelf life, stability and storage at room temperature, and no requirements for reconstitution prior to administration. SMA Testing: There are several genetic tests available that can identify SMA Types 1, 2, and 3.	
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Significant variation in risdiplam pricing globally, with prices ranging from USD $8.82 to $225.07 per mg. The most important component of the manufacturing cost of the drug is the cost of the active pharmaceutical ingredient (API). This cost depends on the price and quantity required. **For risdiplam, the generic API price is expected to be significantly higher compared to other APIs due to its small patient population and low annual dosage. Despite this, the generic price will still be much more affordable compared to its branded version and not present the same level of economic challenges highlighted in the above national and academic cost-effectiveness summaries.** In China Roche's risdiplam is priced drastically lower - thus showcasing that the branded version of the drug is for sale at an affordable price (only 3.8% of the US daily price) and has the potential for more widespread affordability and accessibility. There is a recurring pattern in the different cost-effectiveness and comparative cost evaluations of risdiplam. Risdiplam's high cost, which leads to significant incremental cost-effectiveness ratios, is demonstrated by both national and academic studies. All of the aforementioned health assessment organizations have suggested risdiplam for payment, despite its high cost (albeit with different requirements for this reimbursement).	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? **As of July 2023, there were 2,163 patients that participated in Roche's Compassionate Use Program (CUP) for risdiplam across 59 countries, 23 of these are LMICs.** In many countries, particularly LMIC, **hundreds of children with SMA continue to be born and die or suffer from the burden of comorbidities because they lack access to SMA treatments.** This lack of access results in a significant unmet medical need, where children are deprived of life-altering treatment.	☐ Yes ☒ No ☐ Not applicable

Does the medicine have wide regulatory approval? Risdiplam is approved in over 120 countries for the treatment of 5q spinal muscular atrophy (SMA) in patients from birth or from 2 months of age.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable