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): The application for risdiplam was made by an NGO and supported by three more. The target population is patients with 5q spinal muscular atrophy (SMA) who present with clinical symptoms of SMA types 1, 2, or 3 regardless of the number of SMN2 gene copies, or who possess between one and four SMN2 gene copies regardless of symptom severity. SMA incidence ranged from 5.1 to 16.6 cases per 100,000 live births (depicting a rare condition). Approximately 60% of SMA cases manifest in infancy, resulting in the most severe phenotype and often leading to fatal outcomes within the first two years of life. In about 12–20% of cases, the disease presents after the patient has become ambulatory. The mortality rate for SMA patients also depends on when symptoms manifest. SMA impacts individuals differently depending on the severity but is universally marked by progressive muscle weakness and loss of function. The condition usually affects essential physiological functions, such as swallowing and respiration; nearly all early-onset patients require mechanical ventilation and many require parenteral nutrition. SMA imposes a significant physical, psychological, social, and financial burden on both patients and their families. Risdiplam offers several advantages over other SMA treatments, including the convenience of not requiring refrigeration when in powder form, ease of administration, as it is taken orally once daily after a meal using a provided oral syringe. It may be especially suited for resource-limited settings. However, evidence base for effectiveness is still moderate[1] and outcomes albeit showing clinical improvement, are not supported by statistical significance. Four trials have been done in different disease types and age groups, and comparisons with other treatments, in the absence of head-to-head trials, is done by matching-adjusted indirect comparison (MAIC) methodology, which may bring misleading conclusions[2]. Trials mainly focused on children, and in adults results are insufficient. No long-term safety information exists. Quality of evidence for survival, event-free survival, and serious adverse events was moderate to high, but for improvement of motor function (according to motor function scales) was moderate. For respiratory function, low. Maximal benefits were seen in patients treated before the onset of symptoms[3]. Most studies were observational, single–arm and unblinded, including only a moderate number of patients, and funded by manufacturer[1]. Risdiplam is intented for long-term continuous treatment. Although several important gains are perceived because of oral route and ease of storage, adequate treatment requirements, overall, are huge. The drug is very expensive and not cost-effective without an average 90% cost cut (in countries that have done cost-effectiveness studies), which may be difficult to obtain, because of several patents in more than 120 countries, since 2019. Despite the possibility of a future compulsory license in India, the present scenario is patent-dominated. The effectiveness of treatment is mainly for pre-symptomatic patients (a case study of treatment during pregnancy showed results which cannot be generalized), but newborn screening for SMA occurs in only 2% of the newborns worldwide[4]. Treatment by proxy (according to sibling diagnosis) may be inadequate. In light of this information, I do not recommend inclusion of risdiplam in the EML or the EMLc.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? No alternative medicines are listed on the Model Lists for the treatment of SMA. Notwithstanding the applicant's efforts to motion towards the inclusion of essential products with unaffordable prices, this has not come to fruition. (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? The pool of available evidence is moderate for risdiplam[1] and clinical trials began in 2016[5]. SMA is currently divided into two groups: 5q-SMA and non-5q-SMA. Therapeutic drugs have only been developed for 5q-SMA (nusinersen, onasemnogene abeparvovec, risdiplam) and not for non-5q-SMA disease[6]. In the absence of comparative data between drugs, pre-symptomatic patients (identified via newborn screening – NBS),	☐ Yes ☒ No ☐ Not applicable

newly-diagnosed symptomatic patients under 2 years, and the rest of prevalent cases must be taken into consideration when trying to identify the role of risdiplam in the treatment of SMA[4]. Four clinical trials assessed risdiplam in different age groups and SMA types: FIREFISH (Type I, 62 participants 1-7 months), SUNFISH (II and III; 231 participants 2-25 years), JEWELFISH (174 patients with previous treatment, 6 months to 60 years); the RAINBOWFISH (pre-symptomatic state) trial is ongoing[7]. Comparative data were also collected from children treated with nusinersen who participated in the ENDEAR and SHINE trials. Combined data supported risdiplam as a superior alternative to nusinersen in children with type 1 SMA in an industry-funded study[8]. Risdiplam treatment showed clinically meaningful improvement in motor function compared with the placebo[9], however, except for survival, the significance of improvement was moderate or modest. Trials mainly focused on children. Quality of evidence for survival, event-free survival, and serious adverse events was moderate to high; for improvement of motor function (according to motor function scales) was moderate. For respiratory function, low. Nutritional outcomes were not evaluated. Maximal benefits were seen in patients treated before the onset of symptoms[3]. New SUNFISH data support better motor function for five years after one year of treatment. Outcomes from the studies were compared using matching-adjusted indirect comparison (MAIC) methodology. When direct head-to-head comparisons do not exist MAIC adjusts for differences in baseline characteristics between patients in two trials to make the populations more similar and reduce bias in the comparison[8]. In MAIC publications in SMA to date, the quality of analysis and reporting varied greatly. Various sources of bias in the MAICs were identified, including differences in inclusion/exclusion criteria, imbalances in baseline characteristics, definitions and assessment schedules of outcomes, lack of control for key confounders and effect modifiers, inconsistency in outcome definitions across trials, and lack of reporting key elements. Findings can be misleading, especially in the context of SMA[2]. Other two single-arm interventional studies of presymptomatic treatment (NURTURE and SPR1NT), six observational studies comparing presymptomatic or screened cohorts versus symptomatic cohorts, and twelve follow-up studies of NBS cohorts were also identified. Comparative observational studies supported the finding that presymptomatic treatment, and early treatment following screening, may improve outcomes compared with treatment at the symptomatic stage[10]. Presymptomatic study results may be important in countries where newborn screening for SMA is not available, and siblings of affected children identified prenatally at birth or as presymptomatic may be treated in the first few days of life. However, there may be difficulties in accurate diagnosis, and risk of over diagnosing. Questions persist on long-term efficacy, potential regressions, impact on quality of life and social functioning, therapy duration, and discontinuation indicators. For risdiplam, given its recent approval, more data is required for a comprehensive evidence base[1]. Some studies had insufficient sample sizes to provide robust results[11]. Efficacy in adults constitutes another gap in our current knowledge. The added value of risdiplam in conjunction with other approved medications is still not proven. Older patients have a limited potential for improvement, and current clinical outcome measures are not able to capture minimal changes, especially in a heterogenous population with no standardization of the evaluation across centres, as it is the case in real-world evidence[4].	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? Safety data integrated from the different studies (FIREFISH, SUNFISH, and JEWELFISH trial data), showed no treatment-related safety findings leading to withdrawal from risdiplam treatment (up to 38.9 months in 465 patients). Risdiplam treatment has not led to retinal toxicity in clinical studies[4]. The most common side effects are fever, diarrhea, and rash (in at least 10%) of treated patients with SMA Types 2 and 3. In SMA Type 1 patients, risdiplam-treated subjects	☐ Yes ☒ No ☐ Not applicable

presented with upper respiratory tract infection, constipation, pneumonia, and vomiting (incidence of at least 10%). These conditions are common in untreated SMA Type 1 patients and may not be drug related. Less common adverse events observed during clinical trials in SMA Type 2 and 3 patients included mouth and aphthous ulcers, arthralgia, and urinary tract infection[4]. In animal studies, risdiplam was associated to adverse effects on reproductive organs, including germ cells, in males, but these effects are expected to be reversible upon discontinuation of the drug. There are concerns with potential long-term toxicity, or effects on male fertility and teratogenicity[4]. The most recent EMA recommendation is to stop the drug 4 months before conception in males and 1 month before conception until the end of breastfeeding for females[3]. Risdiplam has an apparent good safety profile. However, gaps remain. First, its safety and pharmacokinetic profile in infants less than 2 months (to be clarified by the RAINBOWFISH study). Second, long-term safety remains unknown.	
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? Since clinical trials of risdiplam only enrolled a small number of SMA adults, the effectiveness and safety of risdiplam for adult patients with SMA should be validated in real-world experiences. There is no head-to-head comparison of current available disease modifying drugs regarding therapeutic effectiveness[12]. For children a more positive outlook exists, with some favorable outcomes and good safety profile. However, uncertainties regarding treatment response and long-term outcomes for patients with SMA remain. Most studies were observational, single–arm and unblinded, including only a moderate number of patients, funded by manufacturer. Conflict of interest of authors potentially compromise validity. Critical long-term outcome measures, such as respiratory function or health-related quality of life (HRQoL), were not sufficiently detailed. Motor function assessments varied across studies and were not consistently reported at baseline and follow-up, which may have resulted in selective reporting, highlighting favorable results[1]. The drug has been authorized through accelerated programs, and the conduction of post-marketing studies is needed as a condition of their marketing approval to better understand their risk–benefit profiles in real-world settings[13]. There may be little incentive to conduct a high-cost multinational trial when the drug has already obtained regulatory approval with a broad label and treatments are already available clinically. Non-inferiority trials are an acceptable alternative, enabling allocation concealment and randomization. Blinding may not always be feasible due to marked differences in treatment schemes. As no direct head-to-head comparison trial between the different treatments is planned and given the high heterogenicity of patients in terms of age and function at baseline, it is very unlikely that strong evidence of superior efficacy of one treatment over another will ever become available[3].	☐ Yes ☒ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Risdiplam is intended for long-term indefinite treatment, and dependent upon the patient's clinical response. The drug should be administered continuously. For SMA, the timing of administration is key to obtain optimal drug efficacy for a disease-modifying treatment, confirmed by the RAINBOWFISH trial. Identifying patients via NBS is a crucial step[14]. Currently, across the world, only 2% of the newborns are screened for SMA, although this number is expected to increase in the future[4]. Several factors such as age at treatment initiation, disease severity, number of SMN2 copy, co-morbidity, and patient/family preference should be considered in treatment decisions[3]. SMA confirmation through genetic testing is required as part of the prescription of risdiplam to patients - except when it is prescribed as a prophylactic treatment. However, prenatal testing and newborn screening are absolutely necessary. Early diagnosis is key for successful treatment. At this point it is impossible to know the type of SMA but number of copies of SMN2 gene may correlates well with potential identification of type[15]. A range of analytical methods can be used, such as qPCR,	☐ Yes ☐ No ☐ Not applicable

ddPCR, PCR-HRM, MLPA, and various SMA testing kits (available commercially). In LMIC contexts, the samples are sent to neighboring countries with the requisite genetic laboratory to run the genetic test. Regular multidisciplinary care is needed for patients with SMA (e.g., physiotherapy, orthopedic management, respiratory management, gastroenterologist support). When treated with risdiplam, patients require clinical evaluations to assess the therapeutic effect and motor function improvements along with safety monitoring, but also to look after other complications associated with SMA. Healthcare professionals, typically pediatric neurologists, with expertise in managing SMA should be responsible for prescribing risdiplam, because they are best equipped to diagnose SMA accurately, assess disease severity, and monitor the treatment response. These specialists are sparse in lower-income settings, where expertise in SMA is scarce and limited to large urban centers which may be too far for some patients to receive a timely and accurate diagnosis and management. The risdiplam powder is dissolved into water, usually by a pharmacist, and the solution must be prepared and accurately measured using the provided oral syringes. The dosing of risdiplam should be after a meal to enhance the drug absorption. Risdiplam does not need to be administered in a hospital. It can be administered in various settings, including at home. This flexibility in administration enhances the accessibility and the Risdiplam can also be given through a gastrostomy tube or a nasogastric tube. For at-home administration, caregivers require some initial training to prepare and administer the drug. Risdiplam oral solution, once reconstituted, should be ideally stored in a refrigerator at 2°C to 8°C and protected from light. It can be kept refrigerated for up to 64 days. If refrigeration is not available, the reconstituted solution is stable at room temperatures, up to 40°C, for a combined total of 5 days. The powder form (unreconstituted medicine) can be stored at room temperature (15°C to 25°C) away from light for up to 12 months, provided it is kept in its carton. In February 2025 a 5mg tablet formulation was approved by the FDA and by PMDA (Japan). This eases dosing in older patients and forgoes need of refrigeration.	
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? There is significant variation in risdiplam pricing globally. Average cost is 150 USD/mg. Price in China is under 10 USD, but outlier and not public price. Despite this localized price reduction, risdiplam is not affordable and remains out of reach for most families. Risdiplam is more more cost-effective than nusinersen. The loading dose of nusinersen currently costs 353,200 euros, whereas 3 months of risdiplam will cost 18,083 euros for a 5-kg baby. However, risdiplam is not yet widely approved in infants younger than 2 months. Cost effectiveness was conducted by some entities and countries, while incorporation and reimbursement decisions were not directly linked to CE, most subject to societal pressures. UK: NICE conducted a cost-effectiveness analysis comparing risdiplam to best supportive care (BSC). The Incremental Cost-Effectiveness Ratio (ICER) for risdiplam compared to BSC was above £50,000 per QALY gained (for SMA Type 1) and significantly higher than £30,000 per QALY gained (for SMA Types 2 and 3) Canada: a cost analysis was done comparing risdiplam to nusinersen and best supportive care (BSC). The analysis focused on QALYs and life-years over different time horizons. The ICER for risdiplam compared to BSC was $1,203,108 per QALY (for Type 1) and $37,378,163 per QALY (for Types 2 or 3) In both cases, substantial price reductions (up to 99%) would be needed to view risdiplam as cost-effective. Netherlands: The Zorginstituut conducted a cost-effectiveness analysis comparing risdiplam to best supportive care (BSC) and nusinersen. The ICER for risdiplam compared to BSC was €362,300 per QALY (for Type 1) and €416,471 per QALY for types 2 or 3. A 89% cost reduction is needed for cost-effectiveness. Ireland: the NCPE recommended that risdiplam not be considered for reimbursement until its cost-effectiveness could be improved.	☒ Yes ☐ No ☐ Not applicable

Australia: Based on the high ICER values and the need for a significant price reduction (up to 85% for certain patient groups), the document suggests that risdiplam at its current price does not offer value for money compared to alternatives like BSC and needs a substantial price reduction to be considered cost-effective. Brazil: Based on this model risdiplam has ICER of R$5,094,220.37 per QALY gained. The annual cost for a patient already in maintenance treatment with the maximum dose of risdiplam versus an equivalent patient on nusinersen is R$761,100.00 versus R$483,138.00. These calculations, however, disregard the costs of supportive care. France: Despite not being cost-effective, HAS has granted a favorable reimbursement status for Types 1, 2 and non-ambulant Type 3 SMA, while excluding reimbursement for Type 4. Portugal, Scotland, New Zealand: no data on cost-effectiveness, but all reimburse or fund. Pharmacoeconomic analyses show that the technology is not cost-effective compared with the best support therapy[16]. Overall budget impact remains substantial due to the high cost of the drug. The cost of blood sample testing can range from 3–5 USD in newborn screening programs to USD 50–500 for individual tests in diagnostic labs.	
Is the medicine available and accessible across countries? The medicines is available in several countries – the manufacturer has actively fostered availability because of favourable drug dosage form and regimen, and also because of high prices, which makes it economically interesting. Risdiplam is under patent. Access worldwide remains very limited. Risdiplam holds potential for a low-cost generic version due to its relatively inexpensive manufacturing process, however, it will be patent protected for many years (until 2041, if no patent extension strategies are implemented which is doubtful); the first patents were filed in 2019. The manufacturer holds relevant risdiplam patents in 120 countries. Requests for voluntary license on three separate occasions have been denied. In late March, 2025 Roche was denied an injunction against a generic manufacturer in India o grounds of public interest, and according to the applicant this would make way for compulsory licensing. As of July 2023, there were 2,163 patients that participated in the manufacturer´s Compassionate Use Program (CUP) for risdiplam across 59 countries, 23 of these are LMICs.	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? Risdiplam is approved in over 100 countries for the treatment of 5q spinal muscular atrophy (SMA) in patients from birth or from 2 months of age (the latter contradicts trials evidence since earlier treatment is best for outcomes, albeit of difficult implementation due to diagnostic constraints). Label extension is being revised by several countries to include patients from 0-2 months. Not listed in the International, British, European, or United States Pharmacopoeia.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable

Additional references

1. Giess D, Erdos J, Wild C. An updated systematic review on spinal muscular atrophy patients treated with nusinersen, onasemnogene abeparvovec (at least 24 months), risdiplam (at least 12 months) or combination therapies. Eur J Paediatr Neurol. 2024 Jul;51:84-92. doi: 10.1016/j.ejpn.2024.06.004.

2. Jiang T, Youn B, Paradis AD, Beckerman R, Barnieh L, Johnson NB. A Critical Appraisal of Matching-Adjusted Indirect Comparisons in Spinal Muscular Atrophy. Adv Ther. 2023 Jul;40(7):2985-3005. doi: 10.1007/s12325-023-02520-2.

3. Ramdas S, Oskoui M, Servais L. Treatment Options in Spinal Muscular Atrophy: A Pragmatic Approach for Clinicians. Drugs. 2024 Jul;84(7):747-762. doi: 10.1007/s40265-024-02051-2.

4. Markati T, Fisher G, Ramdas S, Servais L. Risdiplam: an investigational survival motor neuron 2 (SMN2) splicing modifier for spinal muscular atrophy (SMA). Expert Opin Investig Drugs. 2022 May;31(5):451-461. doi: 10.1080/13543784.2022.2056836.

5. Waldrop MA. Clinical decision making around commercial use of gene and genetic therapies for spinal muscular atrophy. Neurotherapeutics. 2024 Jul;21(4):e00437. doi: 10.1016/j.neurot.2024.e00437.

6. Nishio, H.; Niba, E.T.E.; Saito, T.; Okamoto, K.; Lee, T.; Takeshima, Y.; Awano, H.; Lai, P.-S. Clinical and Genetic Profiles of 5qand Non-5q-Spinal Muscular Atrophy Diseases in Pediatric Patients. Genes 2024, 15, 1294. https://doi.org/ 10.3390/genes15101294

7. Nishio H, Niba ETE, Saito T, Okamoto K, Takeshima Y, Awano H. Spinal Muscular Atrophy: The Past, Present, and Future of Diagnosis and Treatment. Int J Mol Sci. 2023 Jul 26;24(15):11939. doi: 10.3390/ijms241511939.

8. Kokaliaris C, Evans R, Hawkins N, Mahajan A, Scott DA, Sutherland CS, Nam J, Sajeev G. Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy. Adv Ther. 2024 Jun;41(6):2414-2434. doi: 10.1007/s12325-024-02845-6.

9. Qiao, Y.; Chi, Y.; Gu, J.; Ma, Y. Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Brain Sci. 2023, 13, 1419. https://doi.org/ 10.3390/brainsci13101419.

10. Cooper, K.; Nalbant, G.;Sutton, A.; Harnan, S.; Thokala, P.; Chilcott, J.; McNeill, A.; Bessey, A. Systematic Review of Presymptomatic Treatment for Spinal Muscular Atrophy. Int. J. Neonatal Screen. 2024, 10, 56. https://doi.org/10.3390/ijns10030056.

11. Pascual-Morena C, Martínez-Vizcaíno V, Cavero-Redondo I, Martínez-García I, Moreno-Herráiz N, Álvarez-Bueno C, Saz-Lara A. Efficacy of risdiplam in spinal muscular atrophy: A systematic review and meta-analysis. Pharmacotherapy. 2024 Jan;44(1):97-105. doi: 10.1002/phar.2866.

12. Tsai LK, Ting CH, Liu YT, Hsiao CT, Weng WC; Society for Neurological Rare Disorders-Taiwan. Recent Advance in Disease Modifying Therapies for Spinal Muscular Atrophy. Acta Neurol Taiwan. 2024 Sep 30;33(3):81-88. PMID: 39363429.

13. Crisafulli, S.; Boccanegra, B.; Vitturi, G.; Trifirò, G.; De Luca, A. Pharmacological Therapies of Spinal Muscular Atrophy: A Narrative Review of Preclinical, Clinical– Experimental, and Real-World Evidence. Brain Sci. 2023, 13, 1446. https://doi.org/10.3390/ brainsci13101446.

14. Moultrie F, Chiverton L, Hatami I, Lilien C, Servais L. Pushing the boundaries: future directions in the management of spinal muscular atrophy. Trends Mol Med. 2025 Jan 9:S1471-4914(24)00339-3. doi: 10.1016/j.molmed.2024.12.006.

15. Voight S, Arya K. Considerations for Treatment in Clinical Care of Spinal Muscular Atrophy Patients. Children (Basel). 2024 Apr 20;11(4):495. doi: 10.3390/children11040495.

16. Motta-Santos A, Noronha K, Reis C, Freitas D, Carvalho L, Andrade M. Cost-Effectiveness of Technologies for the Treatment of Spinal Muscular Atrophy: A Systematic Review of Economic Studies. Value in Health Regional Issues. 2024 Jul 1;42:100985. doi: 10.1016/j.vhri.2024.02.002.