A.40	Risdiplam – spinal muscular atrophy – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Three leading treatments for SMA, 2 drugs nusinersen & risdiplam, and one gene therapy (onasemnogene abeparvovec, 'Zolgensma') are available. The 3 SMA treatments are effective and very expensive for many patients. But for many patients, there is no access to Zolgensma or they are over the age of 2 and not eligible for Zolgensma. Of the two drugs, risdiplam has several advantages for EML. Nusinersen requires an intrathecal injection every 4 months, while risdiplam is given orally and taken once daily after meals using the oral syringe. Administration of risdiplam does not require hospitalization and can be taken at home. Additionally, risdiplam will most likely have a cheaper generic version available in the near future. This drug is relatively cheap to produce. Regulatory pathways only require proof of bioequivalence. There are countries with GMP manufacturing capabilities where no patents have been applied for or granted for risdiplam. 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 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. An estimated 2 percent of the population are considered carriers. Estimates of 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. SMA Type 1 is considered the most aggressive Type of SMA and is the leading genetic cause of death in early infancy.

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: 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 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. Infants will receive risdiplam for 24 months, followed by a 36-month extension. RAINBOWFISH Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic spinal muscular atrophy: All infants treated for ≥12 months were alive without permanent ventilation, maintained swallowing and feeding abilities, and had not required hospitalization. RAINBOWFISH will provide information about presymptomatic risdiplam administration and will help determine the dose for infants aged <2 months. The RAINBOWFISH study's interim results have led the FDA to expand the indication for risdiplam to include the treatment of presymptomatic infants under 2 months of age with spinal muscular atrophy. 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? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☐ No ☐ Not applicable 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. The FIREFISH open-label extension phase will provide additional evidence regarding long-term safety and efficacy of risdiplam.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
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: 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. SMA Testing: There are several genetic tests available that can identify SMA Types 1, 2, and 3.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: A recent KEI survey found prices in high-income countries ranging from $117 to $232 per mg, or $213,525 to $423,400 annually for a dose of 5mg per day. (30) These prices do not account for non-transparent discounts and rebates to some third-party payers. Roche has offered some access programs in some lower-income countries to make risdiplam more affordable. For example, the approach in India is to limit the number of bottles the patient pays for in any given year, but the price is still very high relative to average incomes. What makes risdiplam a particularly important drug is that, at present, it provides the best chance to make an affordable generic available. Not only is the drug easier to manufacture than nusinersen or the gene therapy onasemnogene abeparvovec, but risdiplam can be distributed in powder form through the mail. Caregivers of persons with SMA or SMA patients can reconstitute the drug in a water-based solution and administer the drug with simple oral/enteral syringes.
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: 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. The prices of the API depend upon the methods used to manufacture the drug as well as the scale of production and the degree of competition among suppliers. At present, there are a number of suppliers of the risdiplam API, which sell small quantities for research purposes. The prices quoted are often for very small quantities, and do not represent the much lower prices that are possible for larger orders. The generic price per API of risdiplam could be significantly higher than the WHO EML median drug price, but would still be low enough to yield a much more affordable version of the drug. Currently, the price of risdiplam per API unit in high-income countries is very high. On an API kilogram basis, Roche prices range from $118 million per kilogram to $209 million per kilogram in high-income countries. Even if the API generic price were an order of magnitude higher than our highest API cost estimate ($400,000), it would still be possible to manufacture and make the drug available for less than 0.5% of the US list price, nationwide without additional insurance or other reimbursements from third parties.

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: