Proposal for the addition of risdiplam to the WHO model lists of essential medicines for the treatment of children and adults with spinal muscular atrophy

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Comments from the Department of Mental Health, Brain Health and Substance Use

Spinal muscular atrophy (SMA) is a debilitating and fatal autosomal recessive neurodegenerative disease characterized by the degeneration of lower motor neurons, skeletal muscle atrophy, and progressive generalized weakness leading to an almost certain early death. A rare disease, SMA is most commonly inherited in an autosomal recessive pattern. Traditionally, phenotypic classifications are recognized and classified as types 0-4 in decreasing severity with types 0 (prenatal) and type 1 (infantile) the most severe and type 4 (adult onset) being the least severe.

This proposal is for the addition of risdiplam, a once daily oral medication used for the treatment of SMA to the WHO EML for children and adults. Risdiplam is one of three disease-modifying treatments used in SMA, the other two being nusinersen, an intrathecal injection, and onasemnogene abeparvovec, an AAV9 gene replacement therapy.

Certain aspects of risdiplam use deserve special consideration. 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. Without treatment, deterioration progresses over time, imposing significant difficulties and challenges on people affected and their families. These challenges are further compounded by the awareness of early mortality as well as a deep sense of injustice when life-saving treatments are beyond reach. Risdiplam offers the potential to slow, halt, or, in many cases, reverse disease progression, preserving motor function and thus transform the lives of people with SMA and their families.

Two major clinical trials have assessed the efficacy and safety of risdiplam in SMA type 1 (FIREFISH) and SMA types 2 and 3 (SUNFISH). In 62 infants with Type 1 SMA, the FIREFISH trial demonstrated that about 60% of patients achieved the primary endpoint of sitting without support for at least 5 seconds after 2 years and 87.1% of patients survived without permanent ventilation by the end of the first year – a dramatic improvement considering that, most often, infants with Type 1 SMA are never able to sit independently and ultimately do not survive without permanent ventilation.

For SMA Type 2 and 3, the SUNFISH randomized, double-blind, placebo-controlled study enrolled 180 people between ages 2 and 25 to determine if there was a change from baseline in the Motor Function Measure 32 (MFM32) score after one year of treatment. People treated (n=120) with risdiplam showed a 1.36-point improvement in MFM32, compared to a -0.19 change in the placebo group (n=60).

The application also presents data examining the primary efficacy and safety data in risdiplam-treated in infants with presymptomatic SMA. RAINBOWFISH was a multicenter, open-label, single-arm study for infants up to six weeks old with genetically confirmed 5q-autosomal recessive SMA, without clinical signs of SMA at baseline. After one year of treatment, 4/5 (80%) infants were able to sit without support for more than 5 seconds (primary endpoint).

Safety data from the study included teething, COVID-19, pyrexia, gastroenteritis, eczema, and constipation. No deaths were reported and no adverse events that led to withdrawal or treatment discontinuation.

WHO currently does not have any guidelines on treatment of SMA, nor is any treatment for SMA currently included in the WHO EML. Risdiplam is approved in over 100 countries for the treatment of SMA from birth or from 2 months of age. Clinical guidelines such as the UK's National Institute for Health and Care Excellence (NICE) recommend risdiplam as an option for treating 5q spinal muscular atrophy (SMA) in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies. Risdiplam is also approved by the US FDA for both children and adults.

Currently, the powder for oral solution 0.75 mg/ml is available and a 5 mg tablet has recently been approved by the US FDA. Risdiplam's oral administration is especially suited for resource-limited settings and has the potential for low-cost generic production due to its relatively inexpensive manufacturing process. While there are few recent studies on cost-effectiveness, pricing data is available from countries. For example, analysis of countries providing risdiplam shows a range of pricing globally between USD $8.82 to $225.07 per mg. The lower price indicated for risdiplam showcases that through negotiation efforts, the price of the medicines can be significantly decreased. In the United Kingdom, NICE conducted a cost-effectiveness analysis comparing risdiplam to best supportive care. The analysis concluded that while risdiplam shows significant clinical benefits, its ICERs are substantially high, indicating that the treatment is not cost-effective at its current price (£7,900 per 60 mg (80 ml) vial). Despite this, NICE ultimately recommended risdiplam for reimbursement by the NHS for treating SMA provided that certain conditions are met, including a confidential discount to its list price.

The feasibility of implementation and use of risdiplam in low resource settings remains a challenge in that genetically confirmed SMA requires capacity and resources to diagnose and treat. These include specialists healthcare workers, laboratories with diagnostic capabilities and healthcare systems with strong supportive services. However, risdiplam's oral administration is especially suited for resource-limited settings and given it's potential to slow, halt, or, in many cases, reverse disease progression, caregiver burden is likely to decrease with administration of this medication.

Additional mechanisms for decreasing the costs of medicines for rare diseases in generally is also addressed at the end of this application. The case for identifying mechanisms to lower costs is of great value but beyond the scope of this review.