30 March 2021

Dear members of SMA Europe,

We are delighted to be able to share with you – as per your request for regular updates – that today the European Commission (EC) has approved Evrysdi™ (risdiplam), the first and only at home Spinal Muscular Atrophy (SMA) treatment with proven efficacy in adults, children and babies two months and older. Risdiplam was reviewed under the European Medicine Agency's (EMA) accelerated assessment programme, intended for medicines that are of major interest to public health and therapeutic innovation.[1]

Today's approval means that risdiplam is now authorised in Europe for the treatment of 5q SMA (the most common form of the condition, representing about 95% of all SMA cases[2]) in patients 2 months and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies. The decision applies across all 27 European Union member states, as well as Iceland, Norway and Liechtenstein.

Less than five years have passed since the first person enrolled in the risdiplam clinical development programme, which is led by Roche in partnership with the SMA Foundation and PTC Therapeutics. Thanks to the determination and resolve of SMA community members, like you, we have been able to accelerate our progress toward today's announcement. Meanwhile, more than 3,000 people are being treated with risdiplam in clinical trials, real-world settings and through the compassionate use programme, which is open in more than 60 countries.

We want to take this opportunity to express our sincere gratitude to the many hundreds of patients and families who are participating in our clinical studies, the patient groups and the clinical trial sites and staff around the world. We thank you for your partnership, the trust you have placed in us and your unyielding commitment to achieve this monumental milestone. Today we celebrate that partnership and our collective achievement.

EC approval follows a positive opinion issued in February by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) and is based on data from two pivotal studies; FIREFISH (in symptomatic infants with Type 1 SMA aged 2 to 7 months) and SUNFISH (in people with Types 2 or 3 SMA aged 2 to 25 years). Both studies have demonstrated the clinically meaningful efficacy and favourable safety profile of risdiplam.

Whilst today marks a significant milestone for the SMA community, we are keenly aware of the persisting unmet need that remains in access to treatment options. Roche is working closely with reimbursement and assessment bodies in European countries to enable broad and rapid access for those in need. Our collaborative efforts and the urgent need to treat SMA have resulted in early access pathways to risdiplam, aligned to the European label, in Germany in the coming days and in France from early April through the cohort Temporary Authorisation for Use (ATU). To minimise any delay between EC authorisation and access to risdiplam, we have already submitted reimbursement dossiers in many European countries in anticipation of today's approval.

At the same time, we continue to work hard to enable broad and rapid access for patients and families worldwide. In less than eight months, risdiplam has received approval in 38 countries across the world (United States, Chile, Brazil, Ukraine, South Korea, Georgia, Russia, United Arab Emirates, the 27 EU member states and Iceland, Norway and Liechtenstein) and we are pursuing marketing authorisation in a further 33 countries (Argentina, Australia, Botswana, Bolivia, Canada, China, Colombia, Costa Rica, Ecuador, Great Britain, Guyana, Indonesia, Israel, Japan, Kuwait, Malaysia, Mauritius, Moldova, Namibia, New Zealand, North Macedonia, Oman, Pakistan, Paraguay, Peru, Qatar, Saudi Arabia, South Africa, Singapore, Switzerland, Taiwan, Thailand and India – where the first step towards approval was granted). We are also planning additional filing in several international countries in the coming weeks and months.

We expect that you may receive questions from your community about today's news, so we have included some additional information below for you and your members. If you have any other questions about this update, please do not hesitate to contact me.

Sincerely,

Fani Petridis

Fani Petridis, on behalf of the Roche Global SMA Team
Senior Global Patient Partnership Director, Rare Diseases (SMA)

**Questions and Answers**

**What is the indication for risdiplam?**
Risdiplam is indicated for the treatment of people with 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies. 5q SMA is the most common form of the disease, representing about 95% of all SMA cases.[2]

**What does EC approval mean?**
EC approval means that risdiplam is now authorised for use in this indication across the 27 EU member states, as well as in Iceland, Norway and Liechtenstein.

**When will risdiplam become available in EU member states?**
Regulatory approval is the first step towards commercial availability. Risdiplam will become available by early April in France (under the cohort Temporary Authorisation for Use), and in the coming days in Germany. Health authorities in other European countries will now decide whether to reimburse risdiplam for use in their national health systems. Roche has already submitted reimbursement dossiers in many of these countries in anticipation of today's approval to minimise any delay between EC authorisation and access to risdiplam.

**Why can't patients below the age of two months receive risdiplam?**
Risdiplam is not approved for use in patients below the age of two months because the dose and the efficacy and safety have not yet been evaluated in these groups of patients. The RAINBOWFISH trial is currently recruiting pre-symptomatic infants up to six weeks of age to assess the efficacy and safety of risdiplam. Families should consult with their treating physician if they are interested in taking part in a clinical trial. More information on the RAINBOWFISH trial (NCT03779334), as well as previously recruiting risdiplam trials, can be found on ClinicalTrials.gov and ForPatient.Roche.com websites.

**What is the safety profile of risdiplam?**
Risdiplam's safety profile has been evaluated across three clinical trials: FIREFISH, SUNFISH and JEWELFISH. In infantile-onset SMA patients, the most common adverse reactions observed in risdiplam clinical studies were fever (48.4%), rash (27.4%) and diarrhea (16.1%). In later-onset SMA patients, the most common adverse reactions observed in risdiplam clinical studies were fever (21.7%), headache (20.0%), diarrhea (16.7%), and rash (16.7%). The adverse reactions occurred without an identifiable clinical or time pattern and generally resolved despite ongoing treatment in infantile-onset and later-onset SMA patients. There were no treatment-related safety findings leading to participant withdrawal from any study.

**Does EC approval affect the ongoing Pre-Approval Access (PAA)/ Compassionate Use (CU) programme?**
PAA/CU programmes allow patients to access treatment where no other treatment options are available and where local regulations permit, before approval. Following EC approval, new enrolments to the risdiplam PAA/CU programme will stop in the 27 EU member states (and also Iceland, Norway and Liechtenstein); exact dates will vary depending on the country. However, as each country has its own national regulations for PAA/CU programmes, there may be some variation between countries. Patients in countries who are already enrolled on the PAA/CU programme will continue to receive risdiplam, as directed by their treating physician. Patients with questions about the programme should contact their physician.

**Will the COVID-19 pandemic have any impact on the supply of risdiplam?**
Throughout the COVID-19 pandemic, our primary focus has been to ensure patient safety, uninterrupted access to treatment and to support the wider community. We are continually assessing the potential implications of COVID-19 on our manufacturing and supply chain operations, and we are monitoring the demand for all our therapies to mitigate potential stock-out risks. Currently, we are not facing any supply or logistics interruptions for risdiplam due to COVID-19. However, we are taking proactive measures in collaboration with our logistics service providers to ensure the delivery of products to/from affected countries and regions remains as stable as possible.

**How many patients have been treated with risdiplam worldwide so far?**
More than 3,000 patients have been treated with risdiplam, in clinical trials, compassionate use and real-world settings, with patients ranging from birth to over 70 years of age and including those previously treated with other SMA-targeting therapies.

**What is the risdiplam clinical development programme?**
The clinical development programme for risdiplam includes four ongoing clinical trials, FIREFISH, SUNFISH, JEWELFISH and RAINBOWFISH taking place in various countries all over the world. The RAINBOWFISH trial is

currently the only study that is still recruiting. The programme is designed to help advance our understanding of the safety and clinical efficacy of risdiplam in a wide variety of individuals who have SMA, from pre-symptomatic infants to adults aged 60 with varying levels of disease severity, including pre-symptomatic, Types 1, 2, and 3 SMA, as well as patients previously treated with other SMA therapies. Roche leads the clinical development programme for risdiplam as part of a collaboration with the SMA Foundation and PTC Therapeutics.

References:


1. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment. accessed 13 March 2021.
2. Arnold WD et al. Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era. Muscle Nerve. 2015;51(2):157-167.