



Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	Risdiplam 0.75 mg/mL powder for oral solution
EAMS indication	Risdiplam is used to treat patients 2 months of age and older with type 1 or type 2 of a genetic disease called 'spinal muscular atrophy' (SMA) who are not suitable for authorised treatments.
Company	Roche Products Ltd.
EAMS number	00031/0011
EAMS Scientific Opinion date	17/09/2020

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to physicians who may wish to prescribe the EAMS medicine under their own responsibility. More information about the scheme can be found here:

<http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

The General Medical Council's guidance on prescribing unlicensed medicines can be found here:

https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

What is risdiplam?

Risdiplam is the active substance of this medicine and is available as a powder for oral solution. Risdiplam interacts with a gene that produces the survival motor neuron (SMN) protein which results in an increase of the amount of functional protein.

What is risdiplam used to treat?

Risdiplam is used to treat type 1 (early onset) and type 2 (later onset) spinal muscular atrophy (SMA) in adults and children 2 months of age and older.

How is risdiplam used?

Risdiplam powder for oral solution, is reconstituted in water before use. The reconstituted oral solution can be given by mouth, but also via nasogastric or gastrostomy enteral feeding tubing unable to swallow liquids.

In adolescents and adults, the daily dose of risdiplam is 5 mg (6.6 mL of the 0.75mg/mL oral solution). In infants and children, the daily dose of risdiplam is determined by the prescriber based on the child's age and weight.

How does risdiplam work?

Risdiplam increases the amount of functional survival motor neuron (SMN) protein by interacting with a gene that encodes for this protein.

How has risdiplam been studied?

In early onset SMA, risdiplam was evaluated in 41 patients who had at least 2 copies of the SMN2 gene in the FIREFISH Part 2 study. There was no control and the dose used was based on the results of the dose finding part of the study. The main measure of effectiveness (how well the medicine worked) was the ability to sit without support for at least 5 seconds and the CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) score. The CHOP-INTEND score is measured in points, based on a patient's ability to perform certain motor functions.

In later onset SMA, 180 patients aged 2 to 25 years were included in a controlled study called SUNFISH Part 2 that evaluated the effect of risdiplam against placebo. The primary measure of effectiveness was based on the Motor Function Measure-32 (MFM32) score which assesses 32 items that scan various motor functions such as ability to roll on the front or to stand.

What are the benefits and risks of risdiplam?

Benefits

Early onset SMA patients are normally unable to sit without support. After 12 months of Risdiplam treatment 29.3% of patients were sitting without support for at least 5 seconds. The scores achieved in the CHOP-INTEND were also higher than normally seen in early onset SMA and 56.1% of the patients achieved a score of 40 or higher which is normally never achieved in natural history. Also 85.4% of patients were free of medical interventions such as tracheostomy or intubation for more than 21 consecutive days.

In later onset SMA, patients who took risdiplam saw an average 1.36 increase in the MFM32 score after one year, compared to a 0.19 decrease in patients on placebo (inactive treatment).

Risks

The most common adverse events (occurring \geq 10% of participants) associated with risdiplam in early onset SMA as reported in the FIREFISH Part 2 study included upper respiratory tract infection, pyrexia and pneumonia, constipation, and nasopharyngitis and rhinitis.

In later onset SMA, the most common adverse events observed in the risdiplam treated patients of the SUNFISH Part 2 study were diarrhoea, rash, and arthralgia.

Why has risdiplam been given a positive Early Access to Medicine Scientific opinion?

SMA is a hereditary disease characterised by the progressive loss of spinal motor neurons leading to muscle weakness and is stated to be the leading genetic cause of mortality in infants and young children.

Currently authorised treatments are given either via intravenous injection (with concomitant corticosteroids) or via delivery into the cerebral spinal fluid (intrathecal injections), which both carry specific risks.

Risdiplam has been made available to patients with type 1 or type 2 SMA who are 2 months of age or older and are not suitable for authorised treatments. It is given orally or via nasogastric or gastrostomy tubing and has been shown to improve motor function in both early and late onset SMA. Considering the high unmet need in this population and the evidence that the benefits outweigh the risks, early access to risdiplam for the patients defined in the scope of the EAMS indication is justified.

What are the uncertainties?

The indication for the EAMS protocol concerns type 1 and type 2 SMA. The safety and efficacy of risdiplam in paediatric patients less than 2 months of age is currently being evaluated in the pre-symptomatic patient RAINBOWFISH study. The company that makes risdiplam will provide additional information when it becomes available.

Are there on-going clinical studies?

Long-term extension of the main studies that evaluated the effect of risdiplam in type 1 and type 2 SMA are ongoing and additional data will be available at a later stage. Further studies evaluating risdiplam are ongoing for treatment non-naïve patients in the JEWELFISH study, and pre-symptomatic patients in the RAINBOWFISH study.

What measures are in place to monitor and manage risks?

A risk management plan has been developed to ensure that risdiplam is used as safely as possible. Based on this plan, the company that makes risdiplam must ensure that doctors and other healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the possible side effects and recommendations for minimising these side effects.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report all side effects experienced by patients receiving risdiplam through the scheme, as well as medication errors, overdose, and pregnancies. They will receive a physician pack and comprehensive training on adverse events prior to starting patients on treatment.

The safety data will be reviewed and reported to the MHRA on a regular basis by the company. Healthcare professionals and patients will also receive guides on using risdiplam to reduce the risk of medication errors.

Patients in the Early Access to Medicines Scheme will receive an alert card from their doctor which informs other healthcare professionals about the scheme and provides contact details for advice. Patients should carry the card with them during risdiplam treatment and for 1 month after their last dose, so that it can be shown if they need treatment or advice from a healthcare professional who is not familiar with risdiplam treatment.

Other information about risdiplam – see EAMS Treatment Protocol