

Risdiplam

Approved indication: spinal muscular atrophy

Evrysdi (Roche)

bottles containing 60 mg in 2 g powder for reconstitution as 0.75 mg/mL oral solution

The most common form of spinal muscular atrophy is due to mutations in a gene located on chromosome 5. This is sometimes referred to as 5q SMA. As a result of the mutation there is reduced production of survival motor neuron (SMN) protein. This leads to progressive muscle weakness. The most frequent type of spinal muscular atrophy (SMA1) presents in babies as hypotonia, poor head control and impaired swallowing. Due to neuromuscular weakness, respiratory support will be needed and life expectancy is usually under two years.

A related gene (SMN2) can produce some SMN protein. However, the molecule is truncated so research has investigated how to produce more functional protein. One option is to use nusinersen, an antisense oligonucleotide which enables SMN2 to produce full-length SMN protein. Another option is risdiplam, a modifier of pre-mRNA splicing which also enables production of full-length protein.

The dose of risdiplam is determined by the age and weight of the child. The oral solution is given once daily. It cannot be mixed with milk and formula and should be given after feeding. Risdiplam can cross the blood-brain barrier. It is metabolised by several enzymes including cytochrome P450 (CYP) 3A4, however no dose adjustments are needed with inhibitors of CYP3A, such as itraconazole. Most of the dose is excreted as metabolites mainly in the faeces. The half-life is approximately 50 hours. There have been no studies of risdiplam in patients with renal or severe hepatic impairment.

The open-label FIREFISH trial is studying risdiplam for the management of 5q-autosomal recessive spinal muscular atrophy in patients with two copies of SMN2. The first part of the trial established that the daily dose for infants should be 0.2 mg/kg. After four weeks this dose had doubled the baseline concentration of SMN protein.¹

In the second part of the trial 41 infants (median age 5.3 months) were assessed after taking risdiplam for 12 months. By then 29% (12/41) of the infants were able to sit unsupported for at least five seconds. Approximately 85% (35/41) were still alive and did not require permanent ventilation. Three infants died from respiratory complications.²

The SUNFISH trial also studied 5q SMA but was double-blind and enrolled older patients (median age 9 years). Based on the first part of the trial, the dose of risdiplam for patients weighing at least 20 kg was 5 mg daily. Risdiplam was given to 120 people while 60 were given a placebo. Efficacy was assessed using the Motor Function Measure (range 0–96). After 12 months this score had increased by 1.36 points from an average of 45.48 in the patients taking risdiplam. In the placebo group the score declined by 0.19 points from a baseline of 47.35. The largest improvement was in younger patients with no improvement in the 18–25 years age group. No patients died.³

The effect of risdiplam on pre-mRNA splicing is not confined to the gene coding for SMN protein. Its effect on other genes may explain some of its adverse effects. Risdiplam was embryo-fetotoxic in animal studies and may reduce male fertility. In the SUNFISH trial adverse effects that were more frequent with risdiplam than with placebo included fever, pneumonia, urinary tract infection, diarrhoea, rash and mouth ulcers.³

Risdiplam may improve the survival of infants compared to historical controls,² but its overall effectiveness is not clear. In the SUNFISH trial there was little difference from placebo for some outcomes. While the difference in the primary end point was statistically significant, it is difficult to interpret the clinical significance of a 1.55 difference on a 96-point scale.³ In the SUNFISH trial the clinicians thought 48% of the patients given risdiplam had improved, but so had 40% of the placebo group.³ Although the approved indication is for the treatment of 5q SMA, risdiplam may not be effective for some types of the disease. As younger patients seem to have the better outcomes, early intervention may have the best chance of a meaningful response. Risdiplam can be used in infants from the age of two months, but its role in pre-symptomatic children is still under investigation. It also remains to be seen if any of the adverse effects, such as retinal toxicity reported in animal studies, appear during long-term therapy. While risdiplam will be easier to administer than nusinersen, which requires lumbar puncture, the role of both drugs will need to be considered in the context of emerging gene therapy for spinal muscular atrophy.

T manufacturer provided the AusPAR and the product information

REFERENCES

1. Baranello G, Darras BT, Day JW, Deconinck N, Klein A, Masson R, et al; FIREFISH Working Group. Risdiplam in type 1 spinal muscular atrophy. *N Engl J Med* 2021;384:915-23. <https://doi.org/10.1056/nejmoa2009965>

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NEW DRUGS

2. Darras BT, Masson R, Mazurkiewicz-Bęłdzińska M, Rose K, Xiong H, Zanoteli E, et al; FIREFISH Working Group. Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls. *N Engl J Med* 2021;385:427-35. <https://doi.org/10.1056/nejmoa2102047>
3. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 2022;21:42-52. [https://doi.org/10.1016/S1474-4422\(21\)00367-7](https://doi.org/10.1016/S1474-4422(21)00367-7)

The Transparency Score is explained in [New drugs: transparency](#), Vol 37 No 1, *Aust Prescr* 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA, the [European Medicines Agency](#) and the [Therapeutic Goods Administration](#).