Nusinersen

Aust Prescr 2019;42:75–6
https://doi.org/10.18773/austprescr.2019.019
First published 28 February 2019

Approved indication: spinal muscular atrophy

Spinraza (Biogen)
single-dose vials containing 12 mg/5 mL solution for injection
Australian Medicines Handbook Appendix A

Nusinersen is an orphan drug approved for the treatment of 5q spinal muscular atrophy. This is a rare genetic disease (approximately 1 in 10,000 births) which presents as progressive muscle weakness and atrophy. Until now, there have been no treatments for this disease.

Spinal muscular atrophy is classified into four types depending on age of onset and motor function:

- type 1 – onset 0–6 months, life expectancy less than 2 years
- type 2 – onset 6–18 months, life expectancy 10–40 years
- type 3 – onset after 18 months, life expectancy adulthood
- type 4 – onset after 5 years, life expectancy adulthood.

Approximately half of patients that present are babies with type 1 disease.

Patients with spinal muscular atrophy have insufficient levels of the survival motor neuron (SMN) protein which is essential for the survival and functioning of motor neurons. This protein is encoded by two genes – SMN1 and SMN2. In spinal muscular atrophy the SMN1 gene is lacking but SMN2 is present so patients produce a truncated form of the protein. Having fewer copies of the SMN2 gene is generally associated with earlier onset of disease and more severe symptoms. Nusinersen is a synthetic antisense oligonucleotide which works by enabling the SMN2 gene to produce a full length SMN protein.

Nusinersen 12 mg is administered by lumbar puncture. It should be given at 0, 2, 4 and 9 weeks followed by a maintenance dose every four months. The drug's terminal half-life in the cerebrospinal fluid is 19–25 weeks and it is mainly excreted in the urine. Nusinersen is metabolised by exonucleases, and drug interactions with the cytochrome P450 system have not been found.

The approval of nusinersen is based on several trials in patients aged from 30 days to 15 years. In babies, motor milestones were measured using scales such as the Hammersmith Infant Neurological Examination (HINE) which included evaluation of kicking, head control, rolling, sitting, crawling, standing and walking. The Hammersmith Functional Motor Scale-Expanded (HFMSE) score was used to assess older children. This scale ranges from 1 to 66 with higher scores indicating better motor function.

A phase III randomised, placebo-controlled trial (ENDEAR) included 121 babies aged seven months or younger with type 1 disease. At baseline, all of them were hypotonic and most had delayed motor function development and limb weakness. After six injections of nusinersen or a placebo (0, 2, 4, 9 weeks then 6 and 10 months), half of those given nusinersen (37/73) had achieved motor milestones compared with none (0/37) of those given a sham injection. In the nusinersen group, 22% of babies developed full head control, 10% could roll over, 8% could sit unaided and 1% were able to stand. At the final analysis, 16% of the babies treated with nusinersen had died compared with 39% treated with a sham injection. A lower proportion of babies who received nusinersen had died or required permanent ventilation compared with those in the control group (39% vs 68%).[1] Improvements in motor milestones were also observed in an uncontrolled phase II trial (20 babies) with open-label 6–12 mg and 12 mg doses of nusinersen.[2]

A second randomised, controlled phase III trial (CHERISH) enrolled 126 children with later-onset disease whose symptoms started after six months of age (type 2 and 3 disease). At baseline, they had a median age of 3–4 years. All of them were able to sit, some could walk with support, but none could walk independently. After 15 months (treatment given at 0, 1, 3 and 10 months), children in the nusinersen group (n=84) had improved by 4 points on the HFMSE scale whereas those in the sham-injection group (n=42) had got worse by 1.9 points. (A change of at least 3 points on this 66-point scale is considered to be clinically meaningful.) The proportion of children who were able to stand independently at 15 months was no different with nusinersen than with the sham injection (1/84 vs 1/42).[3]

Adverse events were similar between the treatment and the control arms. The most common events with nusinersen were fever, constipation, rash, respiratory tract infection, pneumonia, nasopharyngitis and bronchiolitis. Reactions associated with lumber puncture, like headache, back pain, vomiting and post-lumbar puncture syndrome, were also reported.

Thrombocytopenia, coagulation abnormalities and renal toxicity have occurred with other antisense oligonucleotides. Decreased platelet counts and elevated urine protein have been observed in some patients treated with nusinersen so blood and urine testing may be needed before or during treatment.

Nusinersen is the first treatment to be approved for spinal muscular atrophy in Australia. It seems to

improve motor function in babies and children, but it is not yet known if the benefits will be sustained in the longer term and increase survival. Patients who completed the ENDEAR and CHERISH trials have been enrolled in an extension study (SHINE trial) which is planned to continue until 2023 and results have not yet been reported.

TT manufacturer provided additional useful information

REFERENCES

1. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Eng J Med 2017;377:1723-32. https://doi.org/10.1056/NEJMoa1702752
2. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 2016;388:3017-26. https://doi.org/10.1016/S0140-6736(16)31408-8
3. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625-35. https://doi.org/10.1056/NEJMoa1710504

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, and the European Medicines Agency and the Therapeutic Goods Administration.