HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
January 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

SPINRAZA (nusinersen), antisense oligonucleotide

- **High clinical benefit for 5q spinal muscular atrophy types I and II and moderate clinical added value for the therapeutic strategy.**
- **High clinical benefit for 5q spinal muscular atrophy type III but no proven clinical added value for the therapeutic strategy.**
- **Insufficient clinical benefit to justify reimbursement for 5q spinal muscular atrophy type IV.**

Main points

- SPINRAZA has been granted a marketing authorisation for the aetiological treatment of 5q spinal muscular atrophy.
- In 5q spinal muscular atrophy types I and II, its superiority compared to a sham injection procedure has been demonstrated on motor function improvement criteria, assessed on validated scales in two clinical studies, and in terms of survival without ventilation and survival rate in one of the 2 studies.
- In 5q spinal muscular atrophy type III, the data from 2 open-label phase II studies are not sufficient to reach a conclusion in respect of its efficacy, however, a benefit could be expected for some patients.
- The effect of nusinersen has not been studied in patients with 5q spinal muscular atrophy type IV.

Therapeutic strategy

- The treatment of a spinal muscular atrophy patient is multidisciplinary, focusing on neurological, orthopaedic, respiratory and digestive symptoms, and accounting for the psychological and social effects of the disease. This treatment must be put in place as early as possible, in particular for types I and II, so as to anticipate chest and lung complications.

Role of the medicinal product in the therapeutic strategy

SPINRAZA is a first-line treatment to be reserved for patients with spinal muscular atrophy type I having experienced an onset of symptoms after the age of 3 months, and for patients with spinal muscular atrophy type II.

The prescription decision should be discussed on a case-by-case basis:

- for severe spinal muscular atrophy type I, with an onset prior to the age of 3 months, particularly accounting for the presence of severe restrictive respiratory syndrome,
- for early spinal muscular atrophy type III, accounting for ambulation ability,

Decisions to set up and discontinue SPINRAZA treatment, particularly in the event of inefficacy in respect of motor and/or respiratory function should be made at multidisciplinary review meetings in reference centres and centres of excellence for neuromuscular disease.

Failing data, SPINRAZA has no role in the treatment strategy for spinal muscular atrophy type IV.

Clinical data

- The efficacy and safety of nusinersen were assessed in 2 randomised, double-blind phase III studies versus a sham injection procedure, one of these on a patient population with spinal muscular atrophy type I (ENDEAR study) and the other on spinal muscular atrophy type II (CHERISH). Failing a clinically relevant comparator, the sham injection procedure used in the control group helped ensure that the blind was retained as much as possible.
- In the ENDEAR study, 122 patients were included, 81 in the nusinersen group and 41 in the control group.
  The 2 primary endpoints were conclusive, in favour of nusinersen with:
  - 21/51 responders in the nusinersen group versus 0/27 in the control group (41% versus 0%, p<0.0001) in respect of Hammersmith Infant Neurological Examination (HINE) motor function (first primary endpoint),
  - HR = 0.53; $CI_{95\ \%}$ [0.316-0.890]; p = 0.0046 in respect of the risk of death or of being placed on permanent ventilation (second primary endpoint).

  Among the secondary endpoints, analysed according to ranking at the end of the study, the risk of death was reduced significantly in the nusinersen group: HR = 0.372; 95% CI [0.1787; 0.7745]; p = 0.0041).
- In the CHERISH study, 126 patients were included, 84 in the nusinersen group and 42 in the control group.
  Motor function (HFMSE -*Hammersmith Functional Motor Scale - Expanded*), in the intermediate analysis planned in the protocol, exhibited a difference of +5.9 points on a 66-point scale, in favour of the nusinersen group (95% CI [3.7; 8.1]; p = 0.0000002).
  Among the secondary endpoints, analysed according to ranking at the end of the study, the proportion of patients achieving an improvement of 3 points in the motor function score at 15 months was higher in the nusinersen group compared to the control group with a statistically significant difference of 30.5% in favour of the nusinersen group (95% CI [12.74; 48.31]; p = 0.0006).
- In spinal muscular atrophy type III, the data from 2 open-label phase II studies are not sufficient to reach a robust conclusion in respect of the efficacy and safety of nusinersen.
- No data are available from patients with spinal muscular atrophy type IV.
- The adverse events in the 2 phase III studies were mostly respiratory and infectious, associated either with the natural course of the disease or with the method of administration via intrathecal injections and lumbar punctures.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for neurology or paediatrics specialists

Benefit of the medicinal product

- The actual clinical benefit* of SPINRAZA for 5q spinal muscular atrophy is:
  - high for type I, II and III,
  - insufficient for type IV.
- SPINRAZA provides a clinical added value** (CAV III, moderate) for the therapeutic strategy of 5q spinal muscular atrophy type I and II and does not provide any clinical added value (CAV V) for the therapeutic strategy of 5q spinal muscular atrophy type III.
- Approval for hospital treatment within a restricted scope.

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This document was drafted on the basis of the Transparency Committee opinion dated 31 January 2018 (CT-16362) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement".