HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
22 JULY 2020

The legally binding text is the original French opinion version

nusinersen
SPINRAZA 12 mg solution for injection

New assessment

Key points

Favourable opinion for reimbursement in the treatment of pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene.

What therapeutic improvement?

Therapeutic improvement in the treatment of pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene.

Role in the care pathway?

The treatment of patients with spinal muscular atrophy (SMA) is symptomatic and requires a multidisciplinary neurological, orthopaedic, respiratory, gastrointestinal, educational, psychological and social approach. Specialists from reference or expertise centres must coordinate the initiation and continuation of treatment, taking into consideration the following factors: treatment and non-treatment indications, conditions for discontinuation (respiratory function, patient or parent preference, poor tolerance, worsening of health status, lack of efficacy, etc.) and patients' quality of life.

It has been established that treatment must be initiated as soon as possible, particularly in types 1 and 2 SMA in order to anticipate chest and lung complications (nocturnal hypoventilation, unproductive cough, rib cage under-development and deformity, risk of infections).

There is currently no treatment for the pre-symptomatic management of SMA, apart from ZOLGENSMA (onasemnogene abeparvovec) available via a compassionate use programme (ATU dated 15/05/2020), and having been granted an MA on 18/05/2020 in patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene, which the Committee has not yet evaluated.

Role of the medicinal product in the care pathway

Considering:

- efficacy results suggesting a change in the natural course of the disease, particularly in terms of ventilation-free survival, survival and acquisition of motor functions, such as the capacity to sit without support;
- uncertainties with respect to the evolution of these patients, with a more favourable progression than in the absence of treatment, but without curing the disease;
- the intrathecal route of administration;
- the absence of data in patients with four or more copies of the SMN2 gene,

SPINRAZA is a first-line treatment in pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene.

Special recommendations

Due to the complexity of the management of this rare disease, the Committee reiterates that it recommends that decisions to initiate or discontinue treatment with SPINRAZA (nusinersen) be taken at multidisciplinary review meetings in neuromuscular diseases reference and expertise centres.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ 5q spinal muscular atrophy is a serious disease, with types 1 and 2 being life-threatening. Most patients with 2 to 3 copies of the SMN2 gene progress to a type 1 or 2 form.
◗ This is a treatment with curative aim .
◗ The efficacy/adverse effects ratio of SPINRAZA (nusinersen) is high.
◗ There is only one medicinal alternative, available solely via a compassionate use programme: ZOLGENSMA (onasemnogene abeparvovec), reserved for patients with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene. However, the Transparency Committee highlights the fact that it has not yet assessed this drug.
For the other patients with pre-symptomatic 5q spinal muscular atrophy not meeting the criteria for the ZOLGENSMA compassionate use programme, there is no alternative.
◗ SPINRAZA is a first-line treatment in pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene.

Public health impact

Considering:

- the potential seriousness of SMA (spinal muscular atrophy), especially in types 1 and 2 patients, which are life-threatening, generally corresponding to patients with a low number of *SMN2* copies,
- its rarity, with pre-symptomatic diagnosis of 5 patients per year currently, and a type 1 incidence of 0.26/100,000 and a type 2 incidence of 1.23/100,000[Erreur ! Signet non défini.].
- the unmet medical need in the pre-symptomatic treatment of infants and children with 5q spinal muscular atrophy, except in patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene for whom the need is currently partially met by ZOLGENSMA (onasemnogene abeparvovec), only available via a compassionate use programme at present,
- the improved life path compared to the natural course of the disease,
- the impact on the organisation of care due to the need for regular intrathecal administration of the medicinal product, which must be performed in a hospital setting,
- the partial response to the identified need in view of data suggesting a change in the natural course of the disease,

SPINRAZA (nusinersen) is likely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of SPINRAZA (nusinersen) is substantial in the treatment of pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene and at the MA dosages.

Clinical Added Value

Considering:

- **data suggesting a change in the natural course of the disease from a phase 2, non comparative study in pre-symptomatic children with 2 to 3 copies of the SMN2 gene, particularly in terms of:**
  - **ventilation-free survival (primary endpoint) for 21 out of 25 patients,**
  - **survival (for all 25 patients at a median age of 26 months),**
  - **the acquisition of motor functions, such as the capacity to sit without support, for all these children;**
- **follow-up at a median age of 34.8 months demonstrating a more favourable progression in these children than in the absence of treatment, but without curing the disease,**
- **the unmet or partially met medical need (via the cohort ATU for ZOLGENSMA (onasemnogene abeparvovec) reserved for patients with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene) in the pre-symptomatic treatment of infants and children with 5q spinal muscular atrophy,**

and despite:

- **the absence of a robust analysis, with matching compared to siblings, which does not enable a precise estimation of the effect size,**

the Committee considers that SPINRAZA (nusinersen) provides moderate clinical added value (CAV III) in pre-symptomatic infants and children with genetically diagnosed 5q spinal muscular atrophy with 2 to 3 copies of the SMN2 gene.