HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 DECEMBER 2020
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onasemnogene abeparvovec
ZOLGENSMA 2 x 10^{13} vector genomes/mL solution for infusion

First assessment

Key points

Favourable opinion for reimbursement in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 and 2 or pre-symptomatic SMA, with up to 3 copies of the *SMN2* gene.

Unfavourable opinion for reimbursement in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 3.

What therapeutic improvement?

Therapeutic improvement, in the same way as SPINRAZA (nusinersen), in the management of symptomatic patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 as well as in pre-symptomatic patients with 1 to 2 copies of the *SMN2* gene.

No clinical added value in the therapeutic strategy for symptomatic patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 2 as well as in pre-symptomatic patients with 3 copies of the *SMN2* gene.

Role in the care pathway?

Patients with SMA must be treated as early as possible, particularly in the event of types 1 and 2 in order to anticipate respiratory complications. Current management consists of:

- Symptomatic treatment, with a multidisciplinary approach, with the aim of improving quality of life. This includes, in particular, physiotherapy, occupational therapy and respiratory assistance, with, in certain cases, non-invasive ventilation and gastrostomy.
- SPINRAZA (nusinersen), an antisense oligonucleotide administered intrathecally, which increases functional SMN protein production by acting on splicing of the *SMN2* gene. Before the arrival of ZOLGENSMA (onasemnogene abeparvovec), SPINRAZA (nusinersen) was the only treatment with an MA in 5q spinal muscular atrophy.

According to the Committee opinions of 2018 and 2020, SPINRAZA (nusinersen) is a first-line treatment reserved for patients:

- with type 1 SMA whose symptoms began before the age of 3 months,
- with type 2 SMA,
- as well as in pre-symptomatic infants and children with genetically diagnosed SMA with 2 to 3 copies of the *SMN2* gene.

The decision to prescribe the drug must nonetheless be discussed on a case-by-case basis:

- in severe type 1 SMA having started before the age of 3 months, taking into account, in particular, the existence of restrictive respiratory syndrome,
- and in early type 3 SMA, taking into account the walking capacity.

SPINRAZA (nusinersen) has no role in the care pathway for the management of type 4 SMA.

Role of the medicinal product in the care pathway

Considering:

- the efficacy of single IV administration of ZOLGENSMA (onasemnogene abeparvovec) observed in 3 non-randomised, open-label clinical studies, in symptomatic patients with type 1 SMA (with 2 copies of the *SMN2* gene) and in pre-symptomatic patients (with 2 or 3 copies of the *SMN2* gene), particularly in terms of survival without permanent ventilation and the acquisition of the main motor milestones,
- results that suggest a marked improvement compared to the natural course of the disease after 2 years in symptomatic patients but without recovery (persistence of motor and respiratory disability) and with uncertainties with respect to maintenance of the effect of treatment and the longer-term outcome for these patients,
- the significant limitations of the indirect comparison with SPINRAZA (nusinersen), the only other medicinal product with an MA in this indication having been the subject of concomitant development, meaning that it is not possible to accurately determine the role of ZOLGENSMA (onasemnogene abeparvovec) in the care pathway of patients with type I SMA compared to this drug,
- and an efficacy that appears to be extrapolable to patients with a clinical diagnosis of type 2 SMA given the clinical continuum between types 1 and 2 and the pathophysiology of the disease, the mechanism of action of the medicinal product, and despite the absence of data in these patients,

ZOLGENSMA (onasemnogene abeparvovec) is a first-line treatment, in the same way as SPINRAZA (nusinersen), to be used in symptomatic patients with type 1 SMA or pre-symptomatic patients with up to 3 copies of the *SMN2* gene.

In symptomatic patients with type 2 SMA, the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) is a therapeutic option but that SPINRAZA (nusinersen) should be favoured pending data in these patients.

In the absence of data and given a lesser medical need and a non-extrapolable efficacy, ZOLGENSMA (onasemnogene abeparvovec) has no role in the care pathway of patients with type 3 SMA.

Due to the complexity of the management of this disease, the decision to initiate ZOLGENSMA (onasemnogene abeparvovec) treatment should be taken on a case-by-case basis at multidisciplinary team meetings within neuromuscular diseases reference and expert centres belonging to the FILNEMUS network. In addition, in accordance with the SPC, treatment must be initiated and

administered in a hospital environment and supervised by a physician experienced in the treatment of patients with SMA.

In the absence of a robust comparison (direct or indirect) compared to SPINRAZA (nusinersen), and pending the results from the national SMA registry (see paragraph 10 of this opinion), the Committee specifies that the choice of these two treatments should be made taking into account:

- the age of the patients, in a context in which the Committee recalls the need to start treatment with ZOLGENSMA (onasemnogene abeparvovec) as quickly as possible and if possible in pre-symptomatic patients,
- the clinical status of patients, insofar as the Committee reiterates the benefit of preservation of respiratory function and the absence of swallowing disorders for administration of treatment,
- patients' comorbidities in view of the safety profile of each treatment and, in particular, the significant hepatic toxicity of ZOLGENSMA (onasemnogene abeparvovec),
- the different administration methods of these medicinal products,
- the available data for these two medicinal products and their level of evidence,
- as well as the choice of families.

The Committee also highlights that, to date, there is no data with ZOLGENSMA (onasemnogene abeparvovec) in:

- patients with a clinical diagnosis of type 2 SMA, in contrast with SPINRAZA (nusinersen),
- patients with type I SMA and 1 or 3 copies of the *SMN2* gene,
- patients weighing more than 13.5 kg,
- patients treated beyond the age of 6 months,
- and patients who would not previously have been treated with SPINRAZA (nusinersen).

Considering laboratory evidence of liver injury observed in clinical studies and cases of serious clinical hepatitis reported in the literature and by experts, the Committee recommends prior performance of a liver function assessment, as well as close monitoring of liver function and hospitalisation for at least 24 hours in a paediatric high-dependency unit following the administration of ZOLGENSMA (onasemnogene abeparvovec).

Following publication of cases of thrombotic microangiopathy in patients treated with ZOLGENSMA (onasemnogene abeparvovec), the Committee recommends the implementation of kidney function monitoring in all patients (creatinine levels and urine dipstick) as well as testing for haemolysis (schizocytes, haptoglobin and LDH assay) in the event of documented thrombocytopenia.

Longer-term monitoring of patients in the context of a registry (see section 10 of this opinion) is essential to assess the medium to long-term effect of ZOLGENSMA (onasemnogene abeparvovec) on respiratory, motor and cognitive functions, and on mortality and quality of life, as well as its safety.

Finally, the Committee points out that, although observed in clinical practice, the use of SPINRAZA (nusinersen) in patients previously treated with ZOLGENSMA (onasemnogene abeparvovec) has not been assessed in clinical studies and has not been validated by an MA.

Special recommendations

Due to the complexity of management of this rare disease and the risks related to administration of ZOLGENSMA (onasemnogene abeparvovec), the Committee recommends that:

- the decision to initiate treatment should be taken on a case-by-case basis at multidisciplinary team meetings within neuromuscular diseases reference and expert centres belonging to the FILNEMUS network,
- the use of this medicinal product be reserved for hospital physicians specialising in SMA,
- close monitoring of liver function be put in place given the laboratory evidence of liver injury observed in clinical studies and cases of serious clinical hepatitis reported in the literature and by experts,
- kidney function monitoring be implemented in all patients (creatinine levels and urine dipstick) as well as testing for haemolysis (schizocytes, haptoglobin and LDH assay) in the event of

documented thrombocytopenia, given the cases of thrombotic microangiopathy (TMA) reported in patients treated with ZOLGENSMA (onasemnogene abeparvovec),
- and that administration of ZOLGENSMA (onasemnogene abeparvovec) be followed by hospitalisation in a paediatric high-dependency unit for at least 24 hours.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ 5q spinal muscular atrophy (SMA) is a serious life-threatening disease, primarily for types 1 and 2 (for which almost all patients have 1 to 3 copies of the *SMN2* gene) with a significant impact on the quality of life of patients and carers, as has been heavily stressed by patient associations.

◗ This is a curative treatment.

◗ The efficacy/adverse effects ratio is high in the short term in patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 and in pre-symptomatic patients with 1 to 3 copies of the *SMN2* gene given data suggesting a marked improvement compared to the natural course of the disease and despite the persistence of motor and respiratory disability.
Although there is no data in patients with a clinical diagnosis of type 2 SMA, the expected efficacy/adverse effects ratio is also high in these patients due to the disease continuum between types 1 and 2 in terms of pathophysiology and patient characteristics and given the efficacy deemed to be extrapolable by the Committee.
The efficacy/adverse effects ratio has still not been established in these indications in the medium to long-term in the absence of data.
The efficacy/adverse effects ratio has also not be established in patients with type 3 SMA due to a non-extrapolable efficacy and the need for higher doses not studied in the clinical studies.

◗ The only alternative with an MA in the treatment of patients with 5q SMA with a clinical diagnosis of type 1 or 2 SMA or in pre-symptomatic patients with 2 to 3 copies of the *SMN2* gene is nusinersen (SPINRAZA) (see section 05 of this opinion).

◗ ZOLGENSMA (onasemnogene abeparvovec) is a first-line treatment, in the same way as SPINRAZA (nusinersen), to be used in patients with SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA or in pre-symptomatic patients, with up to 3 copies of the *SMN2* gene.
In patients with SMA with a clinical diagnosis of type 2 SMA, the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) is a therapeutic option but that SPINRAZA (nusinersen) should be favoured pending data in these patients.
In the absence of data, given a lesser medical need and a non-extrapolable efficacy, ZOLGENSMA (onasemnogene abeparvovec) has no role in the care pathway for patients with a clinical diagnosis of type 3 SMA. (see section 08 of this opinion).

Public health impact

Considering:

- the seriousness of SMA, which is life-threatening, particularly in types 1 and 2 (patients with 1 to 3 copies of the *SMN2* gene), and a significant impact on quality of life, as has been heavily stressed by patient and user associations,
- the rarity of the disease, with an estimated incidence of between 10 and 20 / 100,000 births, all types combined, of which 60 to 30% are types 1 and 2,
- the identified substantial medical need, primarily in symptomatic patients with a clinical diagnosis of type 1 and 2 SMA and in pre-symptomatic patients with up to 3 copies of the *SMN2* gene,
- the partial response to this need and the improvement in life pathway, considering:
    - the additional impact on morbidity and mortality compared to routine multidisciplinary management in the short term, based on a formalised historic comparison, including in pre-symptomatic patients, but without recovery (persistence of motor and respiratory disability) and with uncertainties with respect to maintenance of the effect of treatment and the longer-term safety profile in the absence of data,
    - the expected impact in terms of quality of life through the simplification of care (mechanical ventilation),
    - and despite the absence of data on cognitive development,
    - and uncertainties concerning its contribution compared to SPINRAZA (nusinersen) given the substantial methodological limitations of the indirect comparison conducted,
- the expected additional impact on the organisation of care considering:
    - the ease of use of the single IV infusion of ZOLGENSMA (onasemnogene abeparvovec) compared to repeated intrathecal administrations of SPINRAZA (nusinersen),
    - and despite the need for close laboratory monitoring and the administration of corticosteroids during and after treatment, the need for a multidisciplinary team meeting, hospitalisation in a paediatric high-dependency unit and regular specialised follow-up,
    - as well as management in an approved facility in accordance with precise criteria,

ZOLGENSMA (onasemnogene abeparvovec) is likely to have an impact on public health, in the same way as SPINRAZA (nusinersen).

Considering all these elements, the Committee deems that the clinical benefit of ZOLGENSMA (onasemnogene abeparvovec) is:

- **<u>substantial</u> in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 and 2 or pre-symptomatic patients, with up to 3 copies of the *SMN2* gene.**
- **<u>insufficient</u> to justify public funding cover in all other clinical situations. in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 3.**

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication "treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 and 2 or pre-symptomatic patients with up to 3 copies of the *SMN2* gene" and at the MA dosage.

Clinical Added Value

Symptomatic patients with a clinical diagnosis of type 1 SMA

Considering:

- **the efficacy of single IV administration of ZOLGENSMA (onasemnogene abeparvovec) observed in two non-randomised studies with external control (STR1VE US and START), conducted in 37 symptomatic patients with type 1 5q SMA with 2 copies of the *SMN2* gene and with an average age of 3.5 months, on clinically relevant endpoints, in particular survival without permanent ventilation and the acquisition of the main motor milestones,**
- **formalised comparison of the results of these studies with the results found in a historic cohort describing the natural course of the disease and the clinical relevance of the improvement observed compared to supportive care:**
  - **survival without permanent ventilation after 13.6 months (90.9% [20/22] vs 25% in the historic cohort),**
  - **the capacity for independent sitting for at least 30 seconds at the age of 18 months (59.1% [13/22] vs 0% in the historic cohort),**
- **long-term follow-up observational data for 13 patients treated in the START study, which suggest the maintenance of motor development milestones after a median follow-up of around 4.5 years, with half of patients without any respiratory support, and although these results need to be interpreted with care insofar as more than 50% of patients (7/13) were receiving treatment with SPINRAZA (nusinersen),**

and despite:

- **the absence of recovery in these patients, in whom a motor and respiratory disability persists, with uncertainties concerning characterisation of this disability at this stage,**
- **uncertainties concerning the medium and long-term efficacy (including on cognitive development and quality of life), given limited follow-up,**
- **uncertainties concerning the contribution of ZOLGENSMA (onasemnogene abeparvovec) in the current care pathway given the concomitant development of SPINRAZA (nusinersen) and due to substantial methodological limitations of the adjusted indirect comparison conducted,**
- **and the safety profile marked by sometimes severe liver injury and the absence of medium and long-term safety data,**

the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) provides moderate clinical added value (CAV III), in the same way as SPINRAZA (nusinersen), in the care pathway of patients with type 1 SMA.

Symptomatic patients with a clinical diagnosis of type 2 SMA

Despite the clinical continuum and the expected efficacy in type 2 SMA, in the absence of data in these patients, the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) provides no clinical added value (CAV V) in the care pathway, excluding SPINRAZA (nusinersen), of patients with type 2 SMA.

Pre-symptomatic patients with a bi-allelic mutation in the *SMN1* gene and 1 to 2 copies of the *SMN2* gene

Considering:

- **the efficacy of single IV administration of ZOLGENSMA (onasemnogene abeparvovec) observed in a non-randomised study (SPRINT), conducted in 29 pre-symptomatic patients with 5q SMA, including a cohort of 14 patients with a median age of 21 days with 2 copies of the *SMN2* gene and liable to develop mainly type 1 SMA,**
- **preliminary data suggesting a modification in the natural course of the disease in these patients, in terms of reaching the milestone of independent sitting (8/14; 57.1%), a clinically relevant endpoint,**
- **the benefit of administering the treatment as early as possible in view of its mechanism of action,**
- **and despite uncertainties with respect to the clinical benefit and the medium and long-term safety, with follow-up of less than 1 year in these patients,**

the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) provides moderate clinical added value (CAV III), in the same way as SPINRAZA (nusinersen), in the care pathway of pre-symptomatic patients with a genetic diagnosis of SMA with a bi-allelic mutation in the *SMN1* gene and 1 to 2 copies of the *SMN2* gene.

Pre-symptomatic patients with a bi-allelic mutation in the *SMN1* gene and 3 copies of the *SMN2* gene

Considering:

- **the heterogeneity of the population of pre-symptomatic patients with 3 copies of the *SMN2* gene, in terms of expected phenotype and hence the medical need (patients liable to develop type 2 SMA preferentially, but also possibly types 1 or 3),**
- **uncertainties with respect to the impact of ZOLGENSMA (onasemnogene abeparvovec) in these patients, insofar as, without treatment, some children with type 2 SMA are capable of standing without assistance (primary endpoint) and that most of the children with type 3 SMA can walk alone (ranked secondary endpoint),**
- **and uncertainties with respect to the clinical benefit and the medium and long-term safety with follow-up of < 9 months.**

the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) provides no clinical added value (CAV V), in the care pathway, excluding SPINRAZA (nusinersen), of pre-symptomatic patients with a genetic diagnosis of SMA with a bi-allelic mutation in the *SMN1* gene and 3 copies of the *SMN2* gene.