SUMMARY

onasemnogene abeparvovec

ZOLGENSMA 2×10^13 vector genomes/mL,

infusion solution

Reassessment

Original French opinion adopted by the Transparency Committee on 10 May 2023

The legally binding text is the original French opinion version

Key points

Favourable opinion for reimbursement only in “the treatment of patients with 5q spinal muscular atrophy (SMA) (biallelic mutation in the *SMN1* gene):

- in pre-symptomatic patients with up to 3 copies of the *SMN2* gene
- with a clinical diagnosis of SMA type 1, 2 or 3”.

What therapeutic improvement?

Therapeutic improvement only in pre-symptomatic patients with 3 copies of the *SMN2* gene.

Role in the care pathway?

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. The use of this medicinal product is reserved for hospital neurologists or paediatricians specialising in SMA.

In the absence of a robust comparison versus SPINRAZA (nusinersen) and EVRYSDI (risdiplam), the Committee specifies that the choice between these three treatments should be made taking into account:

- the age of the patients, in a context in which the Committee recalls the importance of starting treatment with ZOLGENSMA (onasemnogene abeparvovec) as quickly as possible and ideally 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 with, for ZOLGENSMA (onasemnogene abeparvovec) a profile characterised by significant hepatic toxicity and a serious risk of thrombotic microangiopathy (TMA) requiring regular appropriate laboratory monitoring,
- the type of SMA and the number of copies of the *SMN2* gene,
- the different administration methods of these medicinal products, as well as the choice of families.

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

- patients with a clinical diagnosis of SMA type 2, in contrast with SPINRAZA (nusinersen) and ERVYSDI (risdiplam),
- patients with SMA type 1 and 1 or 3 copies of the *SMN2* gene,
- patients weighing more than 13.5 kg,
- patients treated beyond the age of 6 months,
- patients who would previously have been treated with SPINRAZA (nusinersen) or EVRYSDI (risdiplam).

In addition, although observed in clinical practice, there is a lack of precise information concerning the use of SPINRAZA (nusinersen) or EVRYSDI (risdiplam) in patients previously treated with ZOLGENSMA (onasemnogene abeparvovec).

The Committee also reiterates the importance of complying with the measures specified in the SmPC for ZOLGENSMA (onasemnogene abeparvovec) before and during its administration, and during patient follow-up, in particular the immunological, renal and haematological measures (section 4.2 of the SmPC).

In addition to these measures, the Committee recommends that administration of ZOLGENSMA (onasemnogene abeparvovec) be followed by hospitalisation in a paediatric high-dependency unit for at least 24 hours.

Moreover, it once again stresses the importance of the following in all patients:

- kidney function monitoring (creatinine levels and urine dipstick),
- haematological monitoring (complete blood count in the week following infusion, then at regular intervals),
- testing for haemolysis (schizocytes, haptoglobin and LDH assay),
- a complete kidney function assessment in the event of documented thrombocytopenia, given several cases of serious thrombotic microangiopathy (TMA) reported in the first two weeks following administration of ZOLGENSMA (onasemnogene abeparvovec).

Given the cases of acute liver failure reported, including some fatal cases, the Committee highlights the crucial importance of close monitoring of liver function in the event of any elevation in transaminases, until a return to normal and beyond.

Role of ZOLGENSMA (onasemnogene abeparvovec):

- **In pre-symptomatic patients with 1, 2 or 3 copies of the *SMN2* gene**: it is a first-line treatment in the same way as SPINRAZA (nusinersen), given the suggested efficacy versus the natural course of the disease.
- **In patients with SMA type 1**: it is a first-line treatment in the same way as SPINRAZA (nusinersen) and EVRYSDI (risdiplam), given the suggested efficacy versus the natural course of the disease.
- **In patients with SMA type 2**: given the absence of data, but due to the disease continuum between types 1 and 2 in terms of pathophysiology and patient characteristics, and its efficacy deemed to be extrapolable, ZOLGENSMA (onasemnogene abeparvovec) is a therapeutic option in these patients, but SPINRAZA (nusinersen) and EVRYSDI (risdiplam), which have demonstrated an efficacy in these patients, should be favoured.
- **In patients with SMA type 3:** ZOLGENSMA (onasemnogene abeparvovec) has no role in the care pathway, given the absence of data (in contrast with SPINRAZA (nusinersen) and EVRYSDI (risdiplam)), a non-extrapolable efficacy and a lesser medical need compared to SMA type 1 and 2.

Special recommendations

Due to the complexity of management of this rare disease and the risks related to administration of ZOLGENSMA (onasemnogene abeparvovec), in addition to the measures indicated in the SmPC, 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 should be reserved for hospital neurologists or paediatricians specialising in SMA,
- administration of ZOLGENSMA (onasemnogene abeparvovec) should be followed by hospitalisation in a paediatric high-dependency unit for at least 24 hours.

Moreover, it once again stresses the importance of the following in all patients:

- kidney function monitoring (creatinine levels and urine dipstick)
- haematological monitoring (complete blood count in the week following infusion, then at regular intervals),
- testing for haemolysis (schizocytes and LDH assay),
- a complete kidney function assessment in the event of documented thrombocytopenia, given several cases of serious thrombotic microangiopathy (TMA) reported in the first two weeks following administration of ZOLGENSMA (onasemnogene abeparvovec).

Given the cases of acute liver failure reported, including some fatal cases, the Committee highlights the crucial importance of close monitoring of liver function in the event of any elevation in transaminases, until a return to normal and beyond.

Transparency 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 and user associations during previous assessments of medicinal products for SMA.
- This is a curative medicinal product.
- The new data available are not of a nature to modify the Committee's previous conclusions in terms of the efficacy/adverse effects ratio, which remains:
  - High in pre-symptomatic patients with 1, 2 or 3 copies of the *SMN2* gene and patients with SMA type 1 and type 2.
  - Not determined in patients with SMA type 3.
- The role of ZOLGENSMA (onasemnogene abeparvovec) in the care pathway is:
  - As first-line treatment in the same way as SPINRAZA (nusinersen) in pre-symptomatic patients with 1, 2 or 3 copies of the *SMN2* gene;
  - As first-line treatment in the same way as SPINRAZA (nusinersen) and EVRYSDI (risdiplam) in patients with SMA type 1;
  - In patients with SMA type 2, ZOLGENSMA (onasemnogene abeparvovec) remains a treatment option, but treatment with SPINRAZA (nusinersen) and EVRYSDI (risdiplam) should be favoured;
  - Absent in patients with SMA type 3.

Public health benefit

The new data available are not of a nature to modify the Committee's previous assessments. ZOLGENSMA (onasemnogene abeparvovec) is likely to have an additional impact on public health.

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

- **substantial only in the treatment of patients with 5q spinal muscular atrophy (SMA) (biallelic mutation in the *SMN1* gene):**
  - **in pre-symptomatic patients with up to 3 copies of the *SMN2* gene,**
  - **with a clinical diagnosis of SMA type 1**
  - **with a clinical diagnosis of SMA type 2**
- **insufficient in the treatment of patients with 5q spinal muscular atrophy (SMA) (biallelic mutation in the *SMN1* gene) with a clinical diagnosis of SMA type 3, to justify public funding in view of the available alternatives.**

The Committee issues a favourable opinion for maintenance of inclusion of ZOLGENSMA (onasemnogene abeparvovec) solution for infusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use Erreur ! Signet non défini. **only within the scope retained and at the MA dosages.**

Clinical Added Value

The Transparency Committee considers that the new clinical data available are of a nature to modify its initial assessment only in pre-symptomatic patients with 3 copies of the *SMN2* gene.

➔ Pre-symptomatic patients with 3 copies of the *SMN2* gene

Considering:

- previous assessments having demonstrated uncertainties with respect to the clinical benefit and the medium and long-term safety due to the limited follow-up (median follow-up of 14 months) based on interim analyses not scheduled in the protocol of the SPR1NT study,
- the final results of the SPR1NT study suggesting efficacy versus the natural course of the disease in these pre-symptomatic patients having received ZOLGENSMA (onasemnogene abeparvovec) before the age of 6 weeks,
- data from extension studies and registries concerning other types of SMA covered by the indications of ZOLGENSMA (onasemnogene abeparvovec) suggesting maintenance of its efficacy on motor, respiratory or nutritional functions in the long term and in the real world;
- the concomitant development with SPINRAZA (nusinersen);

and despite:

- the safety profile of ZOLGENSMA (onasemnogene abeparvovec) demonstrating serious cases of thrombotic microangiopathy (TMA) and acute liver failure, including some having resulted in the patient's death,
- the absence of data on cognitive development and quality of life,

the Committee deems that ZOLGENSMA (onasemnogene abeparvovec) provides a moderate clinical added value (CAV III) in the care pathway, in the same way as SPINRAZA (nusinersen).

➔ Pre-symptomatic patients with 1 or 2 copies of the *SMN2* gene or with SMA type 1, 2 or 3

Considering:

- the new clinical data available, derived from the final results of the SPR1NT study in pre-symptomatic patients with 2 copies of the *SMN2* gene, extension studies and registries suggesting maintenance of efficacy on motor, respiratory or nutritional functions in the long term and in the real world in pre-symptomatic patients with 1 or 2 copies of the *SMN2* gene and in patients with SMA type 1,
- the absence of clinical data supplied in patients with SMA type 2, but taking into account the disease continuum between types 1 and 2 in terms of pathophysiology and patient characteristics, and its efficacy deemed to be extrapolable,
- the absence of clinical data supplied in patients with SMA type 3 due to a non-extrapolable efficacy and the need for higher doses not studied in these patients,
- and despite the safety profile of ZOLGENSMA (onasemnogene abeparvovec) demonstrating serious cases of thrombotic microangiopathy (TMA) and acute liver failure, including some having resulted in the patient's death, and the absence of data on cognitive development and quality of life,

The Transparency Committee deems that these new data are not of a nature to modify its initial assessment in the following indications:

- **Pre-symptomatic patients with 1 or 2 copies of the *SMN2* gene**

The Committee considers that ZOLGENSMA (onasemnogene abeparvovec) provides a moderate clinical added value (CAV III) in the care pathway, in the same way as SPINRAZA (nusinersen).

- **Patients with SMA type 1**

The Committee considers that ZOLGENSMA (onasemnogene abeparvovec) provides a moderate clinical added value (CAV III) in the care pathway, in the same way as SPINRAZA (nusinersen) and EVRYSDI (risdiplam).

- **Patients with SMA type 2**

ZOLGENSMA (onasemnogene abeparvovec) provides no clinical added value (CAV V), in the care pathway, excluding SPINRAZA (nusinersen) and EVRYSDI (risdiplam).