HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
8 SEPTEMBER 2021

The legally binding text is the original French opinion version

onasemnogene abeparvovec
ZOLGENSMA 2 x 10^{13} vector genomes/mL solution for infusion

Re-evaluation

Key points

Favourable opinion for maintenance of 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.

Due to uncertainties related to serious risks of thrombotic microangiopathy (TMA) and liver injury, the Committee would like to reassess ZOLGENSMA (onasemnogene abeparvovec) within a period of one year from the date of this opinion based, in particular, on data from ongoing studies (clinical and ATU (early access programme)), data from the registry and pharmacovigilance data.

What therapeutic improvement?

The Transparency Committee considers that the new data available is not of a nature to modify its initial assessment:

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?

According to the treatment guidelines, treatment should be started as early as possible - at the pre-symptomatic stage if possible - in order to anticipate complications, in particular 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.

- The curative treatments currently available:

o ZOLGENSMA (onasemnogene abeparvovec), a viral vector using the capsid of a non-replicating, recombinant adeno-associated serotype 9 virus, in which the DNA has been replaced by the cDNA of the human survival of motor neuron (SMN) gene and enabling the expression of the deficient SMN protein, as a single intravenous injection;

o SPINRAZA (nusinersen), an antisense oligonucleotide administered intrathecally, which increases functional SMN protein production by acting on splicing of the *SMN2* gene, and;

o now EVRYSDI (risdiplam), an oral *SMN2* gene splicing modifier that has had a European MA since 26 March 2021.

According to the opinions of the Committee of January 2018 and July 2020 for SPINRAZA (nusinersen) and of December 2020 for ZOLGENSMA (onasemnogene abeparvovec):

- In type 1 SMA and in pre-symptomatic patients with up to 3 copies of the *SMN2* gene, SPINRAZA and ZOLGENSMA are first-line treatments. In the absence of a robust comparison, the choice between these two treatments should be made on the basis of the patient's age, clinical condition and comorbidities, the administration methods and the preferences of the family, or on available data and their level of evidence. For patients with severe type 1 SMA having started before the age of 3 months, the decision to prescribe SPINRAZA should be discussed on a case-by-case basis, taking into account, in particular, the existence of restrictive respiratory syndrome. It should be noted that the experts currently recommend treatment of patients diagnosed at the pre-symptomatic stage with 4 copies of the *SMN2* gene;

- In type 2 SMA, SPINRAZA is the treatment to be favoured, whereas ZOLGENSMA is a treatment option pending data in these patients;

- In type 3 SMA, SPINRAZA is the only treatment option available and the decision to prescribe it should be discussed on a case-by-case basis, taking into account the date of onset of the symptoms and the patient's capacity to walk. The Committee considered that ZOLGENSMA had no role in the care pathway for these patients;

- In type 4 SMA, no treatments are currently recommended. In fact, ZOLGENSMA is not indicated in this clinical type and the Committee considered that SPINRAZA had no role in the care pathway.

Role of the medicinal product in the care pathway

The new data available is not of a nature to modify the role of ZOLGENSMA (onasemnogene abeparvovec) in the care pathway defined by the Transparency Committee in its initial assessment.

ZOLGENSMA (onasemnogene abeparvovec) remains a first-line treatment, in the same way as SPINRAZA (nusinersen), to be used:

- in symptomatic patients with type 1 SMA,
- in pre-symptomatic patients with up to 3 copies of the SMN2 gene.

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

As a reminder, 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) and the serious risk of thrombotic microangiopathy (TMA),
- 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 1 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 previously have been treated with SPINRAZA (nusinersen) or EVRYSDI (risdiplam).

Considering laboratory evidence of very frequent liver injury observed in clinical studies and cases of serious clinical liver injury with acute liver failure reported in the literature during the marketing period 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 several cases of thrombotic microangiopathy (TMA) reported during the marketing period, around 1 week to 10 days following administration of ZOLGENSMA (onasemnogene abeparvovec), the Committee recommends the implementation of kidney function monitoring (creatinine levels and urine dipstick) and a complete blood count in the week following infusion, then at regular intervals, in all patients, as well as testing for haemolysis (schizocytes, haptoglobin and LDH assay) and a complete kidney function assessment in the event of documented thrombocytopenia. The Committee also recommends that clear information be provided to parents and carers concerning the signs and symptoms of TMA, the potential clinical consequences and the procedure to be followed if TMA is suspected.

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) or EVRYSDI (risdiplam) in patients previously treated with ZOLGENSMA (onasemnogene abeparvovec) has not been assessed in clinical studies.

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 very frequent liver injury observed in clinical studies and cases of serious clinical liver injury with acute liver failure reported in the literature, during the marketing period and by experts,
- kidney function monitoring (creatinine levels and urine dipstick) and a complete blood count in the week following infusion, then at regular intervals, be implemented in all patients, as well as testing for haemolysis (schizocytes, haptoglobin and LDH assay) and a complete kidney function assessment in the event of documented thrombocytopenia, given several cases of thrombotic microangiopathy (TMA) reported during the marketing period, around 1 week to 10 days following administration of 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

Considering all of this information and further to debate and voting, the Committee considers:

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.

◗ The proprietary medicinal product ZOLGENSMA (onasemnogene abeparvovec) is a curative medicinal product.

◗ The new data available is not of a nature to modify the Committee's previous conclusions. The efficacy/adverse effects ratio of ZOLGENSMA (onasemnogene abeparvovec) remains 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 also remains high in the short term 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 the medium to long-term in the absence of data.

◗ The alternatives with an MA in the treatment of patients with 5q SMA are nusinersen (SPINRAZA) and risdiplam (EVRYSDI) (cf. section 05 of this opinion).

◗ The new data available is not of a nature to modify the role of ZOLGENSMA (onasemnogene abeparvovec) in the care pathway defined by the Transparency Committee in its initial assessment. ZOLGENSMA (onasemnogene abeparvovec) remains a first-line treatment, in the same way as SPINRAZA (nusinersen) and EVRYSDI (risdiplam), 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, in the absence of data, the Committee considers that ZOLGENSMA (onasemnogene abeparvovec) remains a therapeutic option but that SPINRAZA (nusinersen) or EVRYSDI (risdiplam) should be favoured (see section 09 of this opinion).

Public health impact
The new data available is not of a nature to modify the Committee's initial assessment. ZOLGENSMA (onasemnogene abeparvovec) remains likely to have an additional 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) remains SUBSTANTIAL 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.
As a reminder, the clinical benefit is INSUFFICIENT to justify its funding by the French national health insurance system in patients with type 3 SMA.

The Committee issues a favourable opinion for maintenance of 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 with up to 3 copies of the *SMN2* gene" and at the MA dosage.

Clinical Added Value

The Transparency Committee considers that the new data available is not of a nature to modify its initial assessment.

ZOLGENSMA (onasemnogene abeparvovec) maintains a moderate clinical added value (CAV III), in the same way as SPINRAZA (nusinersen), in the care pathway of:

- **symptomatic patients with a diagnosis of type 1 SMA,**
- **pre-symptomatic patients with a genetic diagnosis of SMA and 1 to 2 copies of the *SMN2* gene.**

ZOLGENSMA (onasemnogene abeparvovec) provides no clinical added value (CAV V), in the care pathway, excluding SPINRAZA (nusinersen), of:

- **symptomatic patients with a diagnosis of type 2 SMA,**
- **pre-symptomatic patients with a genetic diagnosis of SMA and 3 copies of the *SMN2* gene.**