HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
8 SEPTEMBER 2021

The legally binding text is the original French opinion version

risdiplam
EVRYSDI 0.75 mg/ml powder for oral solution

First assessment

Key points

Favourable opinion for reimbursement in the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3.

Unfavourable opinion for reimbursement in patients with SMA with a clinical diagnosis of SMA type 4 and in pre-symptomatic patients.

What therapeutic improvement?

Therapeutic improvement in the management of the disease in patients with 5q spinal muscular atrophy (SMA) with a clinical diagnosis of:

- SMA type 1, in the same way as SPINRAZA (nusinersen) and ZOLGENSMA (onasemnogene abeparvovec),
- SMA type 2, in the same way as SPINRAZA (nusinersen), and
- non-ambulant SMA type 3.

No clinical added value in the therapeutic strategy for ambulant symptomatic patients with SMA type 3.

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vector using the capsid of a non-replicating, recombinant adeno-associated serotype 9 virus, in which the DNA has been replaced by the cDNA of the human survival of motor neuron (SMN) gene and enabling the expression of the deficient SMN protein, as a single intravenous injection;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

Considering:

- the medical need to have access to alternative treatments, mainly in patients with a clinical diagnosis of SMA type 1 or 2, but also in patients with type 3 (including ambulant) due to the administration methods, as reported by patient and user associations and experts;

- the efficacy of risdiplam administered daily by the oral route demonstrated in two phase 2/3 clinical studies (FIREFISH and SUNFISH) in patients with a laboratory diagnosis of SMA and a clinical diagnosis of SMA type 1, type 2 or type 3 (non-ambulant patients);

- exploratory results that suggest a marked improvement compared to the natural course of the disease after two 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 methodological limitations of the adjusted indirect comparisons made versus SPINRAZA (nusinersen) and ZOLGENSMA (onasemnogene abeparvovec) due to their concomitant development, in patients with SMA type 1 and 2, meaning that it is not possible to accurately determine the role of EVRYSDI (risdiplam) in the care pathway, and;

- an efficacy deemed to be extrapolable to ambulant patients with a clinical diagnosis of SMA type 3 given the clinical continuum and the pathophysiology of the disease, the mechanism of action of the medicinal product, and despite the absence of data in these patients;

EVRYSDI (risdiplam) is a first-line treatment, to be used:

- in symptomatic patients with SMA type 1, in the same way as SPINRAZA (nusinersen) and ZOLGENSMA (onasemnogene abeparvovec),

- in patients with SMA type 2 and 3, in the same way as SPINRAZA (nusinersen).

In the absence of data and given an efficacy that it is difficult to extrapolate, EVRYSDI (risdiplam) has no role in the care pathway for pre-symptomatic patients with SMA and up to 4 copies of the *SMN2* gene.

Due to the complexity of the management of this disease, the decision to initiate EVRYSDI (risdiplam) 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 by a physician experienced in the treatment of patients with SMA.

In the absence of a robust comparison (direct or indirect) versus SPINRAZA (nusinersen) and ZOLGENSMA (onasemnogene abeparvovec), and pending the results from the national SMA registry (see paragraph 10 of this opinion), the Committee specifies that the choice between the treatments available should be made taking into account:

- the age of the patients; a context in which the Committee highlights the need to start treatment as soon as possible and, if possible, in pre-symptomatic patients;

- the patient’s general condition;

- patients’ comorbidities in view of the safety profile of each treatment and, in particular, the serious risk of thrombotic microangiopathy (TMA) with ZOLGENSMA (onasemnogene abeparvovec);

- the different administration methods of these medicinal products insofar as the Committee highlights the fact that the daily oral administration of EVRYSDI (risdiplam) may be an interesting option compared to the other administration methods available but that it is not necessarily an advantage in young children for treatment compliance reasons;

- the available data for these three medicinal products and their level of evidence;

- as well as the choice of families and patients.

The Committee also highlights that, to date, there is no data with EVRYSDI (risdiplam) in:

- patients with type 1 SMA and 1 or 3 copies of the *SMN2* gene;
- ambulant patients with a clinical diagnosis of SMA type 3;
- and efficacy data in patients who would previously have been treated with SPINRAZA (nusinersen) or ZOLGENSMA (onasemnogene abeparvovec).

As with the alternatives previously analysed by the Committee, longer-term follow-up of patients in the context of a registry is essential to assess the medium and long-term effect of EVRYSDI (risdiplam) on respiratory, motor and cognitive functions, and on mortality and quality of life, as well as its safety.

Special recommendations

Due to the complexity of the management of this rare disease, the Committee recommends that the treatment decision 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 and that the use of this medicinal product be reserved for physicians specialising in SMA.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ 5q spinal muscular atrophy is a serious disease that is life-threatening, primarily in types 1 and 2 (in 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.

◗ The proprietary medicinal product EVRYSDI (risdiplam) is a curative medicinal product.

◗ The efficacy/adverse effects ratio of EVRYSDI (risdiplam) 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, 2 and 3 given data suggesting a change in the natural course of the disease and despite the persistence of motor and respiratory disability.
The efficacy/adverse effects ratio has not been established in these patients in the medium and long-term in the absence of data.

◗ The only alternatives with an MA in the treatment of patients with 5q SMA with a clinical diagnosis of SMA Type 1, 2 or 3 or in pre-symptomatic patients with up to 4 copies of the *SMN2* gene are nusinersen (SPINRAZA) and onasemnogene abeparvovec (ZOLGENSMA) (see section 05 of this opinion).

◗ EVRYSDI (risdiplam) is a first-line treatment in symptomatic patients with SMA type 1, in the same way as SPINRAZA (nusinersen) and ZOLGENSMA (onasemnogene abeparvovec), as well as in patients with SMA type 2 and 3, in the same way as SPINRAZA (nusinersen).
In the absence of data and given an efficacy that it is difficult to extrapolate, EVRYSDI (risdiplam) has no role in the care pathway for pre-symptomatic patients with SMA with up to 4 copies of the *SMN2* gene (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 reported 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 and 30% respectively are types 1 and 2,
- the identified substantial medical need, primarily in symptomatic patients with a clinical diagnosis of SMA type 1 and 2 and in pre-symptomatic patients with up to 3 copies of the *SMN2* gene,
- the partial response to this identified need given:
    - a demonstrated impact on the motor development of non-ambulant patients with SMA type 1, 2 and 3 revealed in the FIREFISH and SUNFISH studies and despite the inherent limitations of these studies, in particular the absence of comparative data versus placebo in patients with type 1 SMA and the exploratory nature of the results concerning survival, respiratory function or swallowing;

- and despite:
  - the absence of a demonstrated impact on the cognitive development and quality of life of patients with SMA;
  - the lack of long-term efficacy and safety data (> 24 months),
  - the absence of data in patients with 1 copy of the *SMN2* gene, patients who are pre-symptomatic, ambulant and symptomatic with type 3 SMA, symptomatic with type 4 SMA, or in patients previously treated with nusinersen (SPINRAZA) or onasemnogene abeparvovec (ZOLGENSMA),
- an expected additional impact on the organisation of care due to daily oral administration, but which has not been demonstrated to date;

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

Considering all these elements, the Committee deems that the clinical benefit of EVRYSDI (risdiplam) is:

- **SUBSTANTIAL in patients 2 months of age and older with 5q spinal muscular atrophy (SMA), with a clinical diagnosis of SMA type 1, type 2 or type 3;**
- **INSUFFICIENT, in view of the available alternatives, to justify public funding cover in patients with 5q spinal muscular atrophy (SMA) with a clinical diagnosis of SMA type 4 or in pre-symptomatic patients with up to 4 copies of the *SMN2* gene.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in "the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3" and at the MA dosages.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

Symptomatic patients with a diagnosis of SMA type 1

Considering:

- **the efficacy of risdiplam demonstrated in the phase 2/3 non-randomised FIREFISH study in 41 patients with type 1 SMA and 2 copies of the *SMN2* gene on endpoints considered to be clinically relevant, with, in particular:**
  - **a formalised but exploratory comparison of the results of this study with those obtained from a historic cohort describing the natural course of the disease (PNCR cohort) suggesting a clinically relevant improvement compared to supportive care, particularly in terms of acquisition of the ability to sit without support for more than 5 seconds after 12 months of treatment, which was the primary endpoint (29.3% vs 5%);**
  - **exploratory results after 24 months suggesting an improvement in motor functions, although no patients are able to stand and walk on this date;**
- **the medical need to have access to treatment alternatives in this rare disease;**

and despite:

- **uncertainties with respect to the efficacy and safety in the medium and long term given limited follow-up (24 months);**
- **the absence of recovery in these treated patients, in whom a motor and respiratory disability persists, with uncertainties concerning characterisation of this disability at this stage;**
- **the absence of data on relevant survival endpoints, relative to respiratory function, swallowing, as well as cognitive development and quality of life;**
- **uncertainties with respect to the role of EVRYSDI (risdiplam) in the current care pathway given the significant methodological limitations of the adjusted indirect comparisons made versus SPINRAZA (nusinersen) and ZOLGENSMA (onasemnogene abeparvovec);**

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

Symptomatic patients with a diagnosis of SMA type 2 and type 3 (non-ambulant)

Considering:

- **demonstration of the superiority of risdiplam compared to placebo in the phase 3, randomised, double-blind SUNFISH study conducted in 180 patients with SMA type 2 (71%) or non-ambulant type 3 (29%) mainly with 3 copies of the *SMN2* gene (87%), in terms of the Motor Function Measure-32 (MFM32) score at month 12, a primary endpoint considered to be relevant (1.36 vs - 0.19 points; Δ = 1.55; $CI_{95\%}$ [0.30; 2.81]; p = 0.0156) or the RULM score assessing upper limb function, a ranked secondary endpoint (20.91 vs 19.65 points; Δ = 1.59; $CI_{95\%}$ [0.55; 2.62]; p = 0.0469),**
- **the medical need to have access to alternatives for the treatment of this rare disease,**

and despite:

- **a size effect deemed to be modest for the motor function (MFM32) and upper limb function (RULM) endpoints;**
- **the absence of demonstration of the superiority of risdiplam compared to placebo for the HFMSE score and for the forced vital capacity (FVC) respiratory endpoint due to non-significant results;**
- **the heterogeneity of the population included (patients aged 2 to 25 years, with SMA type 2 or 3), limiting the extrapolation of results to clinical practice;**
- **the absence of data on the cognitive development and quality of life of patients;**

the Transparency Committee considers that EVRYSDI (risdiplam) provides a moderate clinical added value (CAV III), in the care pathway:

- **in patients with SMA type 2, in the same way as SPINRAZA (nusinersen), and**
- **non-ambulant patients with SMA type 3.**

Symptomatic patients with a diagnosis of SMA type 3 (ambulant)

Despite the clinical continuum of the disease and the expected efficacy in these patients, in the absence of data, the Committee considers that EVRYSDI (risdiplam) provides no clinical added value (CAV V) in the care pathway for patients with type 3 SMA.