REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Spinraza

2.4 mg/ml - 5 ml solution for injection x 1 vial

Nusinersen

Therapeutic indication(s)	Addition of a new population - use in patients over 18 years of age.
Start/end date of procedure	02.07.2020 – 18.12.2020
Final decision	Change in the therapeutic indication of the medicinal product in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF).

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Spinraza

Health problem

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disease, characterized by degeneration of motoneurons in the anterior horns of the spinal cord, leading to atrophy of the striated muscles of the limbs and spine. Clinical manifestations include inability to achieve basic motor skills, such as the ability to raise one's head, sit, stand, or walk. The clinical picture of the disease varies widely, both as regards age and severity of symptoms, and criteria have been established to classify SMA cases according to these characteristics. Patients with a family history of SMA can be identified by genetic testing before symptoms develop. In addition, neonatal screening for birth control has been introduced in some countries.

SMA is a disease with a spectrum of manifestations and has many subtypes with varying severity of the disease, which are described on the basis of age and motor function, as follows. :

- Type 0: beginning in utero; patients do not survive longer after the first months of birth if left untreated; life expectancy < 6 months
- Type I (or Werdnig-Hoffmann disease): acute childhood SMA; most severe (after Type 0); patients are unable to sit; life expectancy < 2 years
- Type II: chronic pediatric SMA; moderate severity; patients can sit alone, but never stand or walk
- Type III (or Kugelberg-Welander disease): chronic juvenile SMA; patients can stand and walk, but often fall and have trouble climbing stairs
- Type IV: SMA starting in adult age; the mildest form with normal functioning

Patients who can reach and exceed 18 years of age are most often classified as Type 2 and Type 3 SMA.

The treatment and follow-up of patients with SMA requires a multidisciplinary approach and the participation of a multidisciplinary team of specialists.

Nusinersen (SPINRAZA) is a modified antisense oligonucleotide that binds to the intron following exon 7 in SMN2 pre-information RNA. It thus modulates mRNA splicing to include exon 7 and to synthesize more whole-chain SMN protein.

Epidemiological data

The incidence of SMA (all types) ranges from 5.1 to 27.7 per 100,000 live births, with the highest incidence reported in Europe. Among the various subtypes of SMA, SMA Type I has been identified as the most common. The estimated prevalence is 1 to 2 per 100,000 people. For SMA Type I, the estimated prevalence is 0.04 to 0.28 per 100,000 people. For SMA

Types II and III combined, the estimated prevalence is 1.5 per 100,000 people. According to the register of patients in Bulgaria, there are over 90 patients, about 30 of whom are children.

Efficacy data

Nusinersen has a large-scale clinical trial program that covers a wide range of patients with Spinal Muscular Atrophy, including the presymptomatic and types I, II and III. During the studies, patients with spinal muscular atrophy treated with nusinersen showed improvements in motor skills and motor development. The primary endpoints assess safety and tolerability. Efficacy endpoints include a change from baseline in terms of the use of a ventilation device, a percentage of time for ventilation support, and a change from baseline. Real-life post-registration studies with nusinersen for the treatment of adults with spinal muscular atrophy are cited, with real-life experience in adult patients showing that nusinersen treatment stops the natural deterioration seen in untreated patients and leads to mild to moderate improvement in some functional parameters, with increased motor function and independence among treated patients.

Safety data

Nusinersen's well-established, long-term safety profile, confirmed in clinical trials, has been validated in real world clinical practice with data from nearly 10,000 treated patients.

The most common side effects with nusinersen are upper respiratory tract infection, nasopharyngitis, vomiting, headache and constipation. The incidence of serious adverse events (SAE) was lower in the nusinersen than in the sham-controlled procedure (41% vs. 61%). The overall incidence of respiratory, thoracic, and mediastinal adverse events was higher in participants with symptomatic early onset of SMA than in those with symptomatic later onset of SMA, and was similar in nusinersen compared to sham control. The immunogenic response to nusinersen was studied in one study, with 6% of patients developing anti-drug antibodies as a result of the treatment.

Data on comparators

Current treatment is limited to respiratory support, nutritional status, orthopedic considerations and certain non-interventional treatments.

Pharmacoeconomic indicators

Published health technology assessments of governmental institutions intended for the health care systems of other countries

Two positive assessments of the health technology from NICE and IQWIG have been cited.

Applied analysis

Cost-effectiveness and cost-benefit analyses have been applied. The perspective of the analyses is of the paying institution – the NHIF. The time horizon is lifelong. A 3.5% discount of costs and results is applied. Markov's model was used, which describes the course of the disease in late development until the end of life. As a comparator, the best supportive care is selected due to the lack of other treatment for these patients. The incremental ratios for therapeutic outcome (year of life gained) and improvement of the quality of life are above the break-even point. Nusinersen is the first disease-modifying therapy to provide long-term improvements in both motor function and survival by altering the course of SMA.

Subgroup analyses

Not attached.

Cost of the assessed health technology

Direct medication cost, medication administration cost, as well as health care cost have been calculated.

Budget impact analysis

The analysis of the budget impact was conducted from the perspective of a paying institution - the National Health Insurance Fund, and the time horizon is 5 years. The estimated number of patients suitable for treatment with the assessed technology is 20 in the first year, reaching 60 in the fifth year. The introduction of nusinersen in the PDL for patients with late SMA development will lead to an increase in the cost for the paying institution, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

SMA, as a rare disease, has a high social burden, which so far is mainly borne by the family and the patients themselves, who cannot be cared for on their own. Improving their condition will reduce the burden on the family and society. Spinraza is indicated in all forms of spinal muscular atrophy associated with chromosome 5q, regardless of patients' age. Studies have shown its efficacy in stabilizing and improving the motor function in patients over 18 years of age.