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

HEALTH TECHNOLOGY ASSESSMENT

Spinraza

12 mg solution for injection 5 ml (2.4 mg/ml) x 1 vial

Nusinersen

Therapeutic indication	Treatment of 5q spinal muscular atrophy
Start- end of the procedure	17.04.2019 – 27.09.2019
Final decision	Final decision is positive for an inclusion in: - Annex 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF) with ICD codes G12.0, G12.1 and restriction: for persons under 18 years of age; - Annex 2 of PDL for purchase from medical establishments with state and / or municipal participation and under Art. 5 of the Medical Establishments Act.

Summary of the report on the clinical and pharmaco-economic evaluation of the health technology of the medicinal product Spinraza

Health problem

Spinal muscular atrophies (SMAs) are a large group of genetic diseases characterized by degeneration of peripheral alpha motoneurons in the anterior horns of the spinal cord and motor nuclei of the cranial nerves, leading to progressive muscle weakness and atrophy. The most common form of SMA, the so-called 5q SMA, is an autosomal recessive (AR) disease caused by mutations in the gene encoding the survival motor neuron 1 (SMN1) protein located on the long arm of chromosome 5 (5q11.2- q13.3). In about 96% of patients there is a deletion of exons 7 and 8 of the SMN1 gene, in rare cases only exon 7. In 3-4% of cases another mutation is found in combination with the typical deletion. The SMN locus on chromosome 5 also contains the SMN2 gene, which is similar in structure to SMN1. SMN2 is intact in all patients with SMA, with the number of copies varying from 1 to 4 and can determine the severity of the disease. SMN1 encodes the major amount of full-chain SMN protein, while 90% of SMN2 and RNA do not include exon 7, resulting in the synthesis of rapidly degrading SMN protein. This protein is essential for the normal functioning of alpha motoneurons and its deficiency leads to neuronal degeneration and progressive muscle and respiratory weakness.
Based on its clinical course and the achieved motor functions 5q SMA is classified into the following forms:
• SMA type I, in which children cannot sit without support (Pediatric spinal muscular atrophy, type 1 Werdnig-Hoffman)

• SMA type II, in which children can sit but cannot walk (Other hereditary spinal muscular atrophies type II, type III Kugelberg-Welander)

• SMA type III, in which patients can walk (Other hereditary spinal muscular atrophies type II, type III Kugelberg-Welander)

• SMA type IV starting in adulthood

SMA is the leading genetic cause of death in infants and children.

Epidemiological data

The reported prevalence of CMA at birth (all forms combined) was relatively consistent in studies ranging from 8.5 per 100,000 live births to 10.3 per 100,000 live births.
A register of patients with progressive Duchenne and Becker-type muscular dystrophy, spinal muscular atrophy and myotonic dystrophy has been established in Bulgaria. The register was developed by the National Genetic Laboratory and Clinic of Neurology, University Hospital "Alexandrovska", Sofia. Participation is voluntary after providing detailed information to patients and their relatives. According to expert opinions and according to the register in Bulgaria, the patients are over 90, about 30 of them are children, and the rest are over 18 years old.

The main clinical manifestations of the disease include progressive muscle weakness due to loss of alpha motoneurons. Weakness is always symmetrical and more pronounced for the proximal muscles. The spectrum of severity ranges from severe generalized muscle weakness and respiratory failure in the neonatal period in SMA type 1 to mild proximal muscle weakness in type 3 and type 4.
The existence of the so-called SMA type 0 with 1 SMN2 copy and prenatal / neonatal onset. Type 0 or prenatal CMA is a rare type in which babies are born with clinical signs of disease, such as severe joint contractures and respiratory damage, which often lead to the need for mechanical ventilation at or shortly after birth. Such patients, if left untreated, die by 6 months of age. The treatment and follow-up of patients with SMA requires a multidisciplinary approach and the participation of a multidisciplinary team of specialists. It includes pathogenetic therapy with Nusinersen and symptomatic therapy of the various complications that may be observed in different forms of the disease and at different stages of progression.
Nusinersen (SPINRAZA) is a modified antisense oligonucleotide that binds to the intron following exon 7 in SMN2 pre-mRNA. By this way modulates mRNA splicing to include exon 7 and to synthesize more whole-chain SMN protein. This is the first drug approved for the treatment of all forms of 5q SMA. The recommended dose is 12 mg (each vial is 5 ml / 12 mg) administered intrathecally. Therapy begins with four loading doses - three every 14 days and the fourth 30 days after the third. The maintenance doses are then given every four months. In the updated Bulgarian National Consensus for Diagnosis, Treatment and Prevention of Hereditary Neuromuscular Diseases, the medicinal product is recommended for patients with SMA type 1, type 2 and type 3 under 18 years of age.
There are no other alternatives for pathogenetic treatment of SMA in Bulgaria or the EU.

Efficacy data

Nusinersen has a well-developed and detailed clinical trial program that covers a wide range of patients with Spinal Muscular Atrophy, including presymptomatic and types I, II and III. Clinical trials for nusinersen were summarized by presenting the results of NURTURE (CS5 / SM201), ENDEAR (CS3B), CS3A, CS2 / CS12 and CS4 (CHERISH). During the studies, patients with Spinal Muscular Atrophy treated with Nusinersen showed improvements in motor skills and motor development.
Efficacy endpoints evaluated in nusinersen clinical trials focused on three main areas relevant to SMA:

- Motor functions (which includes the main stages of motor development, muscular

muscle strength and function);

- Survival and growth;

- Electrophysiology (CMAP).

However, differences in populations and types of SMA in clinical trials require the use of different assessment tools and endpoints to assess the effect of nusinersen on these disease indicators. The criteria for survival (overall survival and event-free survival) and growth (weight-for-age, weight-for-height, height-for-age, and head circumference for age) are most appropriate for evaluating patients with presymptomatic or early onset, while Compound muscle action potential (CMAP) can be used to measure the state of motor neurons in patients with presymptomatic and early onset (Type I), Type II and Type III.

Study: CS5 / SM201 (NURTURE)
Study design: Open, multicenter, multinational, single-arm study
Results:
Efficacy
• Two patients achieve a primary endpoint of lethal outcome or ventilation in the planned fourth interim analysis.
• The motor skills assessed on the HINE and WHO scale were achieved by most patients treated with nusinersen.
• The percentage of responders (patients who have more categories with improvement than with deterioration in the motor stages of HINE) is 72% on day 64 and 100% on days 183, 302, 365 and 421.
The average overall score on CHOP INTEND at the beginning (n = 25) is 49.0 points, from a maximum achievable score of 64 (range 25-60 points). The mean overall CHOP INTEND score at baseline in patients with two copies of SMN2 was 47.0 points (range 25-60 points); patients with three copies of SMN2, the mean overall start-up score was 51.9 points (range 40-60 points). At the last visit in the study, 7 of 25 patients achieved the maximum achievable score of 64 on CHOP INTEND, which is not achievable in patients affected by Spinal Muscular Atrophy. From baseline to the last study visit, 23 of 25 patients achieved and continued to improve in the overall CHOP INTEND score, which is incompatible with the natural course of Spinal Muscular Atrophy. The majority of patients in the study had an increase of at least 4 points from baseline over the study period.
No patient initially achieves the basic milestones of WHO motor development. By Day 183, patients began to consistently achieve the WHO motor development milestones. By day 365, all assessed patients could sit without support, 47% achieved arm and knee crawling, 71% stood with help, and 47% walked with help.
Treated patients were compared to untreated siblings in terms of achieving age-appropriate motor stages of sitting (approximately 6 months of age or day 183) and walking (approximately 14 months of age or day 421). In this analysis, 9 out of 9 patients treated with nusinersen with an untreated sibling achieved the ability to sit alone, while 1 untreated sibling achieved this basic skill. These data indicate that patients treated with nusinersen show development that is different from that of their untreated siblings and is able to achieve motor skills that are not normally achieved by patients with Spinal Muscular Atrophy.

Irrespective of the natural course of Spinal Muscular Atrophy, all patients continue to grow and gain weight and achieve age-appropriate motor skills.
Safety
• Most side effects are mild or moderate. The most common adverse events were reported in 20% or more of patients receiving nusinersen: upper respiratory tract infection (56%), pyrexia (32%), nasopharyngitis (28%) and cough (24%).

Study: CS3B (ENDEAR)

Study design: Phase 3, multicenter, double-blind, randomized, sham-procedure controlled study

Results:

- Based on the positive results of the pre-defined interim analysis, the study was stopped before its planned end.
- In the final analysis, a significantly higher percentage of patients achieved a motor response in the nusinersen group (51%) compared to the control group (0%).
- At the end of the study (without further definition), the overall proportions of HINE-2 responders increased to 64% in children treated with nusinersen. In the last HINE-2 assessment of children with the sham procedure, there were no responders.
- There is a 47% reduction in the risk of lethal outcome or constant ventilation compared to controls (hazard ratio, 0.53).
- Respiratory outcomes at the end of the study: a lower mean ratio of the smallest quartiles means a decrease in time for maintenance with ventilation in infants treated with nusinersen; serious respiratory adverse events (AEs) observed in infants during the study were less common in infants treated with nusinersen than in infants treated with the sham procedure; treatment with nusinersen significantly reduced the risk of the need for constant ventilation (30%) or any respiratory support (23%) compared to the sham procedure.
- In patients with disease duration below the median baseline, patients treated with nusinersen had a reduced risk of lethal outcome or constant ventilation (76% risk reduction) compared to the control patients.
- Significantly more patients achieved a CHOP INTEND response in the nusinersen group (71%) in comparison to the control group (3%); the difference of 68.53% is statistically significant.
- The results of the study show that the overall ratio of CHOP INTEND responders increased to 90% in the final analysis among nusinersen-treated children who were alive and included in the study.
- Subsequently, patients treated with nusinersen had an increase in each growth parameter.

- Sustained and clinically significant increases in the mean CMAP amplitude of the peroneal nerve were observed in the nusinersen group compared to the control group.

Hospitalizations: Babies treated with Nusinersen spent significantly less time in the hospital as a whole and were significantly less often hospitalized for respiratory reasons than infants treated with the sham procedure.
Safety Outcomes: Adverse reactions reported in at least 20% of patients in each group were: pyrexia, constipation, upper respiratory tract infection, pneumonia, respiratory distress, respiratory failure, atelectasis, vomiting, acute respiratory failure, pyrexia, oxygen saturation decreased, cough, dysphagia.

Study: CS3A

Study design: Open, phase 2

Results:

HINE-2

- The change from baseline to the last HINE-2 visit is also significant for the 12 mg group as a whole.
- At the last visits, gradual improvements were observed in 16 of 19 patients; 1 of 4 patients in the 6/12 mg group and 15 of 15 patients in the 12 mg group compared to baseline.
- Improvements of ≥ points were observed in 13 patients for more than one CHOP INTEND category
- The overall average improvement from baseline at the last visit was 11.5 points.
- 12 of 14 patients in the 12 mg group showing an improvement in CHOP INTEND showed an increase from baseline to the last visit (mean increase, 15.2 points).
- A score > 40 was observed in 7 of 13 patients with two copies of the SMN2 gene at the last visit in the 12 mg group.

CMAP

▪ In the 12 mg group, all patients showed an increase in peroneal CMAP at the last visit compared to baseline.

▪ 12 of 15 patients in the 12 mg group showed an increase in ulnar CMAP at the last visit compared to baseline.

▪ Statistically significant increase in CMAP amplitude is:

- peroneal CMAP amplitude: mean increase of 742% or 1.56 mV

- ulnar CMAP amplitude: mean increase of 377% or 0.62 mV

Event-free survival

▪ No mean age for lethal outcome or constant ventilation was reached during the interim analysis.

Safety

▪ A total of 570 adverse events were reported in 100% of patients during the study.
▪ Most adverse events were mild (63%) or moderate (27%) in severity.
▪ All serious adverse events reported in 16 patients were unrelated or unlikely to be related to the study medicine.

Research:

CS2 / CS12

Study design:

CS2 - Phase 1/2a, open-label, multicenter, multiple-dose, dose-escalation study

CS12 - Phase 1, multicenter, open-label, multiple-dose extended study of CS2 or CS10 performed in patients with later onset of Spinal Muscular Atrophy

Results:

Key Results (CS12)

▪ Hammersmith Functional Motor Scale – Expanded (HFMSE) results show a small fluctuation of the mean changes compared to baseline (ranging from 0.29 to 1.27) and are generally stable over the study period. The results showed that 25.5% of patients had a 3-point or greater increase from baseline for 3 or more consecutive visits, while 8.5% had a 3-point or greater decrease from baseline for 3 or more consecutive visits.
▪ Motor function in immobile patients, measured by the Upper Limb Moldule (ULM), showed that patients were stable in upper limb function (range 0.26 to 0.96 during the study), only 1 patient showed a decrease of 2 or more points compared to the baseline for 3 or more consecutive visits. ULM Spinal Muscular Atrophy Results showed that mean baseline changes were generally greater at most time points for patients with Spinal Muscular Atrophy Type II than for patients with Spinal Muscular Atrophy Type III, which may reflect the "ceiling effect" in patients with spinal muscular atrophy type III.
▪ Myometrial results generally show maintenance of muscle strength over time.
▪ CMAP results show that patients have stable muscle electrophysiology during the study.
▪ PedsQL results show that patients generally have stable HRQOL responses; there are no distinguishable patterns for positive or negative mean changes. In general, patients give higher ratings than their parents.

The results of ACEND showed that the impact on caregivers as a whole was constant during the study.

Safety

Adverse events reported in > 20% of CS12 patients include the following:

▪ Upper respiratory tract infection: 44.7%
▪ Headache: 31.9%
▪ Post-lumbar puncture syndrome: 29.8%
▪ Back pain: 25.5%

▪ Pyrexia: 23.4%
▪ Scoliosis: 23.4%

Study: CHERISH Study (CS4)
Study design: Phase 3, randomized, double-blind, sham-procedure controlled study of nusinersen in patients with a later onset (most likely type II or III development) of Spinal Muscular Atrophy
Results:
HFMSE

▪ Nusinersen-treated patients showed a statistically significant improvement in HFMSE scores compared to patients in the control group at month 15. The results for the mean change in the least squares show an improvement in HFMSE results from baseline to month 15 in the nusinersen group of 3.9 and a decrease in the control group of -1.0.
▪ In the nusinersen group, there was a higher percentage of responders who achieved an increase of 3 points or more in the HFMSE score compared to the control group (56.8% vs. 26.3%) at month 15.
▪ More patients in the nusinersen group reached major stages of motor development compared to those in the control group (19.7% vs. 5.9%).

Upper limb module test

The results of the ULM test show a greater improvement in baseline results at month 15 in the nusinersen group compared to the control group (mean change of least squares by 4.2 and by 0.5, respectively).
▪ PedsQL results show improvements in HRQOL in physical function for both groups, as well as patient communication in the control group at later time points as reported by parents. Some patients fill in the questionnaires for themselves and in general their results are higher than those of their parents.
The results of ACEND show that in patients in the nusinersen group the responsibilities of caregivers decrease for the areas of nutrition / hygiene, relocation and mobility, while in patients in the control group the burden of caregivers increases in these areas.

Safety

▪ Nusinersen is well tolerated by repeated intrathecal injection. No specific safety concerns have been identified.
▪ The most commonly reported side effects are respiratory and / or infections.

Study: CS 11 (SHINE)

Study Design: Open-label Extension Study for Patients with Spinal Muscular Atrophy Previously Participating in Nusinersen Studies (CS3A, ENDEAR [CS3B], CHERISH [CS4], or CS12)

Results: The analysis was integrated based on the initial clinical and extended study (SHINE); for the interim analysis as SHINE continues and some patients have limited intake

Results for early-onset SMA (patient who switched from ENDEAR):
Survival / constant ventilation

49% of patients previously treated with nusinersen and 80% of patients previously treated with sham control had lethal outcome or needed constant ventilation at the date of the last data. Within ENDEAR, the median time to death or constant ventilation was 22.6 weeks among participants receiving sham control; in SHINE, the median time to death or constant ventilation was much longer, at 73.0 weeks.
HINE-2 motor skills and CHOP INTEND
Participants in early-onset spinal muscular atrophy who begin nusinersen in ENDEAR and continue in SHINE have seen further improvements in general and specific HINE-2 motor skills, such as head and sitting control and general motor function as measured by CHOP INTEND.
Of the participants who received nusinersen in ENDEAR and SHINE, 28% achieved full head control and 15% independent sitting as the greatest motor achievement; neither participant has yet been able to stand on their own or walk on their own, although patients acquire key skills in both categories.

Results in SMA with later onset:
WHO motor skills
The majority of patients in both CHERISH treatment groups maintained the WHO motor skills they achieved at the start of the initial clinical trial.
The proportion of patients who had previously taken nusinersen in CHERISH who had reached new stages of motor development was higher than that of patients who received sham control.
Mean HFMSE values in patients who had previously received nusinersen increased over time for patients who had previously received nusinersen in CHERISH and were unchanged in patients who had previously received sham control.

Mean HFMSE values in patients with sham control

Patients who had previously received sham control in CHERISH had a mean (median) improvement in the CHERISH baseline of 1.4 (1.0) points in HFMSE, which showed a rapid effect after initiation of nusinersen, in contrast to the decline normally seen in natural course of Spinal Muscular Atrophy.

29% of patients who had previously received sham control in CHERISH had a ≥ 3-point improvement during the initial clinical trial, and 35% who had been evaluated in SHINE had a clinically significant improvement.

6MWT

The results show continued improvement in mobility in patients with Spinal Muscular Atrophy type III from the CS2 study, which is incompatible with the natural course of the disease.

Safety

Nusinersen is well tolerated by repeated intrathecal injections. No specific safety concerns have been identified. The adverse reactions reported generally correspond to the types and severity of adverse reactions observed in infants and children with Spinal Muscular Atrophy or to those associated with the lumbar puncture procedure.

Safety data

The most commonly reported ADRs observed during clinical trials can be systematized by frequency:

- Nervous system disorders - Headache (Very common);
- Gastrointestinal disorders - Vomiting (Very common);
- Musculoskeletal and connective tissue disorders - Back pain (Very common).

Post-marketing experience
Adverse reactions have been reported with post-marketing experience with Spinraza. A serious infection, such as meningitis, has been observed in patients treated with Spinraza by lumbar puncture. Communicating hydrocephalus has also been reported. The frequency of these reactions is unknown.

Immunogenicity
The immunogenic response to nusinersen was studied in 249 patients with post-baseline plasma samples tested for anti-drug antibodies. 16 patients (6%) developed anti-drug antibodies as a result of treatment, of which 3 were transient and 13 were considered resistant. There are insufficient data to evaluate the effect of antibodies on clinical response, adverse events or the pharmacokinetic profile of nusinersen.

Comparators data

Prior to Nusinersen's approval, there was no medicine or effective therapy to modify SMA, and current treatment is limited to respiratory support, nutritional status, orthopedic considerations, and some non-interventional treatments.

There is limited evidence of adherence to care standards; however, studies by different groups of physicians show that there are differences in the use of noninvasive and invasive ventilation.

Pharmacoeconomic indicators

Published assessments of health technology performed by state institutions for the purposes of another national health care system

Ratings from the UK, France, Germany are presented, all of which are positive, but certain conditions are set when prescribing the drug, and in Sweden since 2017 Nusinersen is reimbursed for pediatric patients under 18 years of age with spinal muscular atrophy.

Applied analysis

In the analysis were used cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). An economic model based on the prototype with data for Bulgaria has been developed. Survival and overall survival (OS) from the ENDEAR clinical trial and extrapolation after follow-up of survival in patients with SMA were used as outcome measures. For type II disease, additional analysis from the ENDEAR and CHERISH studies was used. Quality of life was assessed through the pediatric quality of life assessment questionnaire and through the EQ-5D.

Nusinersen was compared in the SMA type I with the placebo arm in the ENDEAR study and against long-term real-life observational data. In SMA type II and III, nusinersen was compared with the placebo arm of the CHERISH study and with long-term real-life observation data. In SMA type III-IV nusinersen was compared with data from long-term observation in real conditions. Real-world care includes supportive symptomatic treatment of reduced respiratory, nutritional, and orthopedic functions.

The perspectives of the society and the payer are presented. The results present the payer's perspective, which includes direct medical expenses (primary and secondary care) and PSS (personal and social services). The time frame of the model starts from the beginning of the therapy to the end of life, and the duration is different for the different severity of the conditions, but at least 20 years are accepted for follow-up. Several variants of the model with discounting 0%, 3% and 5% have been developed.

Three Markov models have been developed with a transition from disease states for the three types of disease severity. The models follow the development of the disease with a gradual loss of vital functions, as well as changes in the inclusion of a particular type of care - respiratory support, support of physical functions and others.

Treatment with nusinersen in patients with type I SMA prolongs survival by 9 years per patient if the results are not discounted and by 5 years if they are discounted at a 5% discount rate. The quality of life also increases by almost 8 QALY if the results are not discounted, and

by almost 5 if they are discounted. The maximum percentage of patients who developed basic motor functions was 55.2% with a mean treatment time with nusinersen of 12 years.
As the analysis was prepared only from the point of view of the National Health Insurance Fund, it does not include the main costs of current care, which are paid by social and other health funds. Nusinersen treatment, when compared to real-world care, increases survival and costs in patients with type I SMA, with QALY increase of 5 and 4.47, respectively.

When patients with SMA Type II and III were treated with nusinersen, overall survival increased by 5 years if results were not discounted and by 1 year if discounted. QALY increased by 19 for patients, respectively by 4.5 for patients and caregivers with undiscounted results, and at discounting - by 6 for patients and by 1.77 for patients and caregivers. Patients treated with nusinersen achieve health with improved motor function, which requires less care and less resource use. The mean duration of treatment with nusinersen was 21 years, during which time 54% of patients with type III achieved maximum motor improvement, in contrast to patients treated with standard care - during this period 10% reached maximum motor improvement. Therefore, the overall health costs are reduced in patients treated with nusinersen.

All three types of models were tested with a deterministic sensitivity analysis, which showed that the cost of the drug and the quality of life of the patients were the factors that most strongly influenced the incremental ratio.

Analyzes of subgroups

The three subgroups of the disease are considered separately and are separate parts of the main analysis, as the data for type I are independent, and for type II and III are together.

Costs for the assessed health technology

Costs for treatment with the product and for routine care are presented. The costs for ordinary care are divided according to the type of care, and some of them are covered by the NHIF, the fund for treatment of children abroad and the parents.

Budget impact amalysis

The analysis of the budget impact was conducted from the point of view of the paying public institution - the National Health Insurance Fund. The costs of the new health technology are included, as well as other direct medical costs. The time horizon is 5 years - from the beginning of drug therapy to the 5th year. The expected number of patients with SMA is at a frequency of 1.21 per 100,000 people.

The level of reimbursement of the new technology will be 100% and the bidget impact is based on the level of reimbursement 100%. The analysis shows that Nusinersen treatment leads to increased costs for the paying institution, depending on the number of patients who

turn to the NHIF system, without taking into account risk-sharing agreements and patient access schemes.

Moral and ethical aspects related to the use of new health technology

Spinal muscular atrophy is a severe genetic disease that begins in childhood, leading to rapid disability and lethal outcome, and is a heavy burden on patients, affected families, and society. So far, there is no cure for this disease and patients are progressing rapidly with a high mortality rate, and families are bearing the full economic burden. The inclusion of nusinersen in PDL will make it possible to slow down the course of the disease, reduce the degree of disability and the economic burden on families and society.

Conclusion

Spinal Muscular Atrophy is a rare, genetic, progressive neuromuscular disease leading to death in infants and children. In the absence of other treatment for patients with SMA, nusinersen is vital for these patients due to its proven efficacy, safety and increase in quality of life. The administration of nusinersen leads to an increase in the life-years gained and the quality-adjusted life years. The costs for the paying institution will increase when the medicinal product is included in the PDL, but the total health costs will decrease due to the reduction of the disability and the economic burden on the patients and their families.