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

HEALTH TECHNOLOGY ASSESSMENT

Translarna

125 mg granules for oral suspension x 30 sachets

250 mg granules for oral suspension x 30 sachets

ataluren

Therapeutic indication(s)	Indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older.
Start/end date of procedure	01.08.2019 – 30.09.2020
Final decision	Inclusion 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 Translarna

Health problem

Duchenne progressive muscular dystrophy is a hereditary neuromuscular disease caused by mutations affecting the dystrophin (DMD) gene, which is manifested clinically with progressive muscle weakness through severe disability, respiratory insufficiency, cardiomyopathy, and in some cases mental retardation and dwarfism. The disease is typical of males. In rare cases due to inactivation of the X chromosome, carrying the dystrophin gene without mutations, it is possible that women carriers will have clinical symptoms that are milder than those in males.
The dystrophin gene is located on the X chromosome at the Xp21 locus and is one of the largest genes in the human genome.

The disease is classified into five main stages:

- Presymptomatic – the majority of boys with Duchenne PMD are not diagnosed during the presymptomatic stage, unless there is a familial involvement or if elevated levels of CPK, AST and ALT are not detected on another occasion.
- Early ambulatory stage in childhood, in which patients have preserved independent gait, there are signs of mild proximal muscle weakness.
- Late ambulatory stage - walking becomes more difficult and more problems appear when climbing stairs and getting up from squatting.
- Early non-ambulatory stage - in adolescence.
- Late non-ambulatory stage - in adulthood.

Duchenne progressive muscular dystrophy is a severe debilitating disease, which ends fatally in the 3rd-4th decades of life and is a serious medical and social problem for patients and their families.

The main goals of the complex therapy, carried out by a multidisciplinary team of specialists in patients with Duchenne-type PMD are the prolongation of the period of preserved independent gait, postponement of complications, such as joint contractures, scoliosis, respiratory and heart failure, impaired gastrointestinal motility.

Translarna is indicated for the treatment of patients with Duchenne-type PMD caused by nonsense mutation in the dystrophin gene, in patients aged 2 years and older, in the ambulatory stage. Efficacy has not been demonstrated in patients who have lost the ability to walk. The presence of a nonsense mutation in the dystrophin gene should be ascertained by genetic testing - direct sequencing of the dystrophin gene.

Epidemiological data

The incidence of Duchenne PMD is estimated at about 1 in 3,500 live male births. In 30% of them mutation occurs de novo, and in other cases it is inherited from the mother.

Mutations responsible for Duchenne PMD are classified as: deletions (about 60% of the cases), duplications (about 8%), point mutations (about 30%). Nonsense mutations belong to the group of point mutations and lead to premature occurrence of stop codon, as a result of which dystrophin is synthesized, which is rapidly degraded and is practically non-functional. According to epidemiological data, they account for 11% of cases with Duchenne type PMD.

The Bulgarian Patient Register for Duchenne/Becker PMD, established in 2009, is part of the TREAT-NMD network. The total number of patients in the register is 172. Of them patients with Duchenne PMD are 136. There are a total of 16 patients with nonsense mutations, of whom 7 boys and one woman symptomatic carriers with preserved independent gait.

Efficacy data

Study 007 was a multicenter, randomized, double-blind, placebo- controlled phase II study. The study included patients over 5 years of age in with a confirmed nonsense mutation in the DMD gene. The use of corticosteroids was allowed. The participants in the study were divided into 3 arms:

- Ataluren - 20-, 20-, 40-mg / kg (high dose) - 60 patients
- Ataluren - 10-, 10-, 20 mg / kg (low dose) - 57 patients
- Placebo - 57 patients

The primary endpoint in Study 007 was the distance covered in 6 minutes (6MWD), estimated at 48th week. The results show that in patients taking 40 mg ataluren daily the distance covered was 42.6 meters versus 12.9 meters with placebo (difference of 29.7 meters). In the adjusted ITT population, the results were 44.1 and 12.8 meters respectively (difference of 31.3 meters). Secondary endpoints indicate that with respect to timed function tests (TFT), patients treated with ataluren had a smaller increase in the 4 stair climb time, 4 stair descent time and 10 meter walk/run time versus placebo. In the group of patients in whom the initial values of 6MWD < 350 meters, the results are more favorable in terms of the time it took to walk/run 10 meters, 4 stair climb time and 4 stair descent time. The results are similar in the group of patients in late ambulatory stage.

Study 020 was a multicenter, randomized, double-blind, placebo-controlled phase III study. The study included patients aged 7-16 years with phenotypic expression of dystrophinopathy (onset of clinical symptoms before 6 years of age, elevated levels of CK, difficulty walking),

confirmed nmDMD, systemic use of corticosteroids at least 6 months before the start of the study; results from 6MWD ≤ 150 meters. Patients are stratified by age (under and over 9 years), duration of corticosteroid use (6-12 months and over 12 months) and 6MWD initial values (below 350 meters and above 350 meters). The participants in the study are randomized 1:1 in 2 arms - patients taking ataluren at a dose of 40 mg/day for 48 weeks and patients on placebo for 48 weeks. The primary endpoint in the study was defined as the ability of ataluren to slow disease progression as measured by a change in 6MWD score. The results of the study show that the change in 6MWD, estimated by the change in the mean values were -47.7 m for ataluren and -60.7 m for placebo (difference 13 meters). The most significant effect was observed in the group of patients with 6MWD ≥ 350 meters.

Secondary endpoints: during 48 weeks in patients treated with ataluren the decrease in muscle function is lesser, as seen in the lesser increase in 10 meter run/walk time, 4 stair climb and 4 stair descent in the ataluren-treated group compared to placebo.

Study 030 is an open-label study, evaluating the safety of ataluren in patients with nmDMD aged 2-5 years for a period of 28 weeks. All patients took ataluren at a dose of 40 mg/kg daily for a period of 4 weeks to evaluate pharmacokinetic parameters and for another 48 weeks to evaluate the efficacy and safety. The cohort of the largest prospective multicenter study on the course of DMD was used for the control group, which includes more than 400 ambulatory and non-ambulatory patients for a period of 10 years.

The results of the study show an improvement in the 10 meter run/walk time (8.9%), 4 stair climb (18%), 4-stair descent time (28%) and time to rise from the floor (43%) in ataluren patients.

Study 025 (Stride) is a multicenter, prospective, observational study of patients treated with ataluren. Data from STRIDE show that in ambulatory patients, ataluren has a beneficial effect on the reduction of respiratory function.

Safety data

The safety profile of Ataluren is based on aggregate data from two randomized, double-blind, 48-week placebo-controlled studies, performed in a total of 232 male patients with Duchenne muscular dystrophy, caused by nonsense mutation (nmDMD) treated with the recommended dose 40 mg/kg/day (10, 10, 20 mg/kg; n = 172) or at a dose of 80 mg/kg/day (20, 20, 40 mg/kg; n = 60), compared to placebo-treated patients (n = 172). The most common adverse reactions in both studies are vomiting, diarrhea, nausea, headache, upper abdominal pain, flatulence, all of which occurred in ≥5% of patients treated with ataluren. In both studies, 0.43% of patients treated with atalurene discontinued treatment due to the adverse reaction

constipation and 0.58% of patients treated with placebo discontinued treatment due to the adverse reaction disease progression (loss of the ability to walk).

An open study was conducted to evaluate FC and the safety of ataluren, in which patients aged 2-5 years were included. In patients aged 2-5 years, a higher incidence of malaise (7.1%), pyrexia (42.9%), ear infection (28.6%) and rash (21.4%) were reported compared with patients 5 years of age and older. However, these conditions are generally reported more frequently in younger children. Safety data for 28 weeks of treatment show a similar safety profile of ataluren in patients 2-5 years of age and in patients 5 years of age or older.

Adverse reactions are generally mild or moderate in severity and serious treatment-related adverse reactions have not been reported in patients treated with ataluren in these 2 studies.

Data on comparators

There are no mutation-specific and effective therapeutic alternatives in patients with Duchenne-type PMD with nonsense mutations.

Pharmacoeconomic indicators

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

Health technology assessments were performed by state institutions of France (HAS), the United Kingdom (NICE), Germany (IQWiG) and Sweden (TLV), with positive decision by all of them.

Applied analysis

A cost-benefit pharmacoeconomic analysis was performed. The main outcome measure is the quality adjusted life years (QALY). The analysis was performed from the perspective of the paying institution - the National Health Insurance Fund, the time horizon is lifelong. Costs and results have been discounted by 3.5% per year. Currently, ataluren is the only authorized drug therapy for patients with nmDMD aged over 2 years who have not lost their ability to walk. The main comparator in the analysis is the best supportive care. According to therapeutic guides, the best supportive care for the target population includes treatment with corticosteroids.

The cost-benefit analysis is based on a semi-Markov model that tracks the progression of patients through a series of health conditions. The model is based on the natural course of disease and includes 6 mutually exclusive health conditions.

The results show that as the disease progresses, the quality of life of patients deteriorates. The largest reduction of quality of life is between the ambulatory and non-ambulatory stages.

The results of the analysis show that ICER values exceed the threshold for value efficiency of 3 times the gross domestic product of Bulgaria. Ataluren has an orphan drug status and treatment costs are high. A probabilistic sensitivity analysis was conducted, the results show that the point at which ataluren therapy will be discontinued (loss of walking ability) and the discount rate are of utmost importance for ICER determination.

Subgroup analysis is not attached.

Costs for the assessed health technology
Only ataluren medication costs were included in the analysis.

Budget impact analysis
The budget impact analysis was performed from the point of view of the paying institution - the National Health Insurance Fund. The time horizon is 5 years. The estimated size of the target population is 10 patients in the first year, reaching 14 patients in the fifth year. Sensitivity analysis was also performed.

Inclusion of Translarna in the Positive Drug List will result in a positive budget impact at the first year of the analysis, gradually increasing through the fifth year, without taking into account risk - sharing agreements and patient access schemes.

Conclusion

Duchenne progressive muscular dystrophy is a severe debilitating disease, which begins in early childhood and ends fatally in the 3rd-4th decades of life and represents a serious medical and social problem for patients and their families. The quality of life of patients with Duchenne PMD is significantly impaired, especially in the later stages of the disease. Translarna is an orphan drug for oral administration for the treatment of patients with Duchenne PMD with nonsense mutations in the dystrophin gene who are in the ambulatory (early and late) stage, i.e. in whom independent gait is preserved. Translarna is the only therapy for treatment of progressive Duchenne muscular dystrophy caused by nonsense mutations in the dystrophin gene.