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

HEALTH TECHNOLOGY ASSESSMENT

Nexviadyme

100 mg powder for concentrate for solution for infusion x 1 (vial)

INN Avalglucosidase alfa

Therapeutic indication(s)	For long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).
Start/end date of procedure	27.04.2023 – 08.12.2023
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases reimbursed by the National Health Insurance Fund (NHIF). Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act, and reimbursement by the NHIF.

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

Health problem

Pompe disease, also known as Glycogen Storage Disease Type II (GSDII), is a rare autosomal recessive neuromuscular disorder affecting people of all ages. Known as acid maltase deficiency, it was the first lysosomal storage disease discovered. The gene responsible for synthesizing the enzyme acid α-glucosidase (GAA) is located on the long arm of chromosome 17, with over 500 known mutations. Lysosomal GAA catalyzes the breakdown of glycogen into glucose. Deficiency of acid α-glucosidase in Pompe disease leads to glycogen accumulation in multiple tissues. In infantile-onset Pompe disease (IOPD), GAA enzyme activity is either completely or nearly absent (usually <1% of normal activity in skin fibroblasts). Some residual enzyme activity (approximately 2-40% of normal activity in skin fibroblasts) is present in most children and adults with late-onset Pompe disease (LOPD). Glycogen accumulation in lysosomes damages their membranes, causing dispersion of hydrolytic material into the cytoplasm and damaging muscle contractile units.

Infantile-onset Pompe disease (IOPD) appears after birth or within the first few months of life, characterized by cardiomyopathy and muscle hypotonia, and may result in death within the first year. Other symptoms include eating problems, poor weight gain, respiratory issues often complicated by lung infection, and delayed motor development.

Late-onset Pompe disease (LOPD) can manifest at any age from early childhood to adulthood. Practically all children with symptoms after age 2 have no significant cardiac manifestations, exhibit slower muscle disease progression, and have a milder prognosis than infantile cases. Major limitations in daily activities for late-onset Pompe disease include the need for ventilatory support and wheelchair use.

Nexviadyme (avalglucosidase alfa) is a new rhGAA enzyme replacement therapy indicated for long-term enzyme replacement therapy for treating patients with Pompe disease (acid α-glucosidase deficiency). Avalglucosidase alfa is a recombinant human acid α-glucosidase (rhGAA) that provides an exogenous source of GAA.

Epidemiological Data

The approximate disease frequency is often cited as 1 in 40,000 but recent newborn screening (NBS) for Pompe disease reveals a much higher frequency. In Bulgaria, 8 patients with the late form of Pompe disease have been diagnosed up to date.

Efficacy data

The therapeutic efficacy and safety profile of Avalglucosidase alfa have been analyzed in four clinical trials.

- Clinical Trial NEO1: A Phase 1, multicenter, multinational, open-label trial to assess avalglucosidase alfa treatment in patients with late-onset Pompe disease aged ≥18 years, both treatment-untreated and previously treated. In adults with late-onset Pompe disease, previously untreated or treated with Myozyme, avalglucosidase alfa (5, 10, and 20 mg/kg) is generally safe and well-tolerated.

- The NEO-EXT clinical trial (NCT02032524) to evaluate the long-term safety and exploratory efficacy of avalglucosidase alfa is a multicenter, multinational trial of avalglucosidase alfa in patients with Pompe disease who completed NEO1. Patients were either treatment naïve or had received Myozyme for ≥9 months (treatment switch group). All patients in NEO1 received intravenous infusions of avalglucosidase alfa every second week at doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for 24 weeks. The results of the trial, taking into account the natural progression of late Pompe disease (decrease in respiratory function) and the long-term decrease in forced vital capacity observed in patients with LOPD treated with avalglucosidase alfa, show sustained functional improvement. Other measures of respiratory function, peak inspiratory pressure, peak expiratory pressure, also remained stable during this period, although there was greater inter-patient variability. Avalglucosidase alfa has been shown to provide sustained benefit in patients with LOPD. In patients treated with avalglucosidase alfa over a treatment period of up to 6 years, there was a stabilization of research parameters of respiratory and motor function. The results were similar regardless of whether patients had received prior Myozyme treatment or not. The sustained results obtained are in contrast to the decrease in efficacy demonstrated with Myozyme administration over a long period of time.

- The COMET clinical trial (NCT02782741) phase 3, multicenter, international, randomized, double-blind trial in patients with LOPD aged ≥ 3 years. The aim of the trial was to evaluate the efficacy and safety of avalglucosidase alfa compared to Myozyme in patients with LOPD. Results showed that avalglucosidase alfa produced improvements compared to baseline in motor function (as measured by the 6MWT) that were continuous and sustained beginning at week

13 and continuing through week 49. Patients treated with avalglucosidase alfa demonstrated a clinically meaningful benefit in mobility as evidenced by the change from baseline in 6MWT to week 49 compared to Myozyme-treated patients. Overall, avalglucosidase alfa demonstrated a more favorable safety profile than Myozyme, and safety results for avalglucosidase alfa were comparable to those seen in the NEO1 and NEO-EXT studies.

- The Mini-COMET clinical trial (NCT03019406) is a multistage, multicenter, international, open-label, dose-escalating, phase 2 cohort trial evaluating the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa in 22 previously treated with Myozyme patients with infantile form. The small sample size for this trial was influenced by the low incidence of IOPD and the limited number of children who could participate. Results showed a trend toward improvement in motor function over the 25-week treatment period, despite heterogeneity between cohorts observed at baseline. There was no detectable decrease from baseline in echocardiographic results of LVM - Left Ventricular Mass Z-score, which was used to measure cardiac function. The safety results in Mini-COMET are similar to the established safety profiles of avalglucosidase alfa and Myozyme. No treatment-related deaths leading to treatment discontinuation were reported for any patient in the trial.

Safety data

Serious adverse reactions reported with Nexviadyme include shivering (1.4%) and headache, dyspnea, respiratory distress, nausea, skin discoloration, chest discomfort, pyrexia, increased blood pressure, increased body temperature, accelerated heart rate and decreased oxygen saturation, each occurring in 0.7% of patients. Hypersensitivity reactions were reported in 43.5% of patients, anaphylaxis in 1.4%, and infusion-associated reactions (IAR) in 26.1%. A total of 2.9% of patients receiving Nexviadyme in clinical trials permanently discontinued treatment. The most commonly reported adverse drug reactions (ADRs) (>5%) were pruritus (9.4%), rash (8%), headache (7.2%), urticaria (6.5%), fatigue (6.5 %), nausea (5.8%) and shivering (5.1%).

Data on comparators

The main comparative alternative is Myozyme (alglucosidase alfa) - the first enzyme replacement therapy (ERT) for Pompe disease with recombinant human acid α-glucosidase (rhGAA).

Pharmacoeconomic indicators

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

Two positive evaluations from HTA agencies of other countries are presented - NICE (Great Britain) and HAS (France).

Applied analysis

A pharmacoeconomic cost-utility analysis (CUA) was applied. Data are also presented for a cost-effectiveness analysis (CEA), where the final outcome in terms of health benefits is presented as quality-adjusted life years (QALYs). Myozyme (alglucosidase alfa) was chosen as a comparative alternative. The perspective is from the point of view of the paying institution - the National Health Insurance Fund (NHIF). The time horizon is lifetime (100 years). Costs and results are discounted at an annual discount rate of 3.5%. A survival model was applied. Three age groups were included in the main analysis: 0–2, 2–16 and 16–100. The estimated ICUR (BGN/QALY) in patients with IOPD for Nexviadyme (avalglucosidase alfa) was above the conditional cost-effectiveness threshold of 60,636.00 BGN/QALY. In patients with LOPD - ICUR (BGN/QALY) compared to the alternative Myozyme (alglucosidase alfa) is above the conditionally accepted profitability threshold of BGN 60,636.00. For the Bulgarian health care system, the assessed health technology is not cost-effective.

Subgroup analyses

No subgroup analyzes were performed.

Costs for the assessed health technology

The analysis describes costs of therapy with the evaluated health technology, costs of the comparative alternatives and other costs - of application.

Budget impact analysis

The analysis of the budget impact was carried out from the point of view of the paying institution - NHIF. The time horizon of the analysis is 5 years. The expected number of patients between 1 and 18 years in the first year is 1, and of patients over 18 years – 6. In the fifth year, the number of patients between 1 and 18 years is 2, and of patients over 18 years - 9. The budget impact analysis was conducted, developing 2 scenarios "World with Nexviadyme" and "World without Nexviadyme". The results show that reimbursing Nexviadyme for long-term enzyme replacement therapy for patients with Pompe disease will result in additional costs for NHIFs within the five-year period of analysis, excluding risk-sharing agreements and patient access schemes.

Conclusion

Nexviadyme is an enzyme replacement therapy clinically studied in children and adults with Pompe disease and with established advantages over the currently available Myozyme enzyme replacement therapy. Nexviadyme provides clinically meaningful improvements in respiratory function, quality of life and safety profile in patients with late-onset Pompe disease (LOPD) compared to Myozyme. In the therapeutic algorithm, Nexviadyme is not a cost-effective alternative compared to Myozyme, as its incremental cost-effectiveness ratio exceeds the upper cost-effectiveness threshold. The budget impact analysis indicates that including Nexviadyme in the therapeutic regimen for Pompe disease will generate additional costs for NHIF over the five-year period.