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

HEALTH TECHNOLOGY ASSESSMENT

Ngenla

Ngenla 20 mg/ml - 1.2 ml solution for injection x 1 pre-filled pen

Ngenla 50 mg/ml - 1.2 ml solution for injection x 1 pre-filled pen

INN Somatrogon

Therapeutic indication(s)	Ngenla is indicated for the treatment of children and adolescents aged 3 years and older with growth disorders due to insufficient secretion of growth hormone.
Start/end date of procedure	26.04.2023 – 21.12.2023
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.

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

Health problem

Growth hormone (GH) is a peptide that is produced and secreted by the anterior pituitary gland (adenohypophysis) at varying rates throughout the day. It is stimulated by a releasing hormone produced in the hypothalamus. Once in the circulation, the GH stimulates the production of insulin-like growth factor 1 (IGF-1) in the liver and growth cartilage. GH and IGF-1 play a key role in childhood growth, in the regulation of lipid metabolism, and in the development of muscle and bone mass. GH deficiency is due to disorders in the function of the pituitary gland or hypothalamus and is classified according to the cause into: **Idiopathic** - lack of an established cause for its deficiency, this is the most common form (82.8% in the USA, 77.1% in Europe); **Acquired** - can be a result of various causes damaging the pituitary-hypothalamus (trauma, radiation, brain tumor, inflammation), the frequency of which is 7.8% in the USA, 12.2% in Europe, respectively; **Congenital** - as a result of congenital genetic diseases (9.4% of cases in the USA, 10.8% in Europe).

Growth hormone (GH) deficiency in childhood manifests itself with retardation in height growth and bone maturation. In newborns, hypoglycemia, jaundice, accumulation of fatty tissue in the abdominal area, reduction of muscle mass can be observed, and in boys - small testicles. In untreated children, the volume of the left ventricle may be reduced, and its systolic function may be impaired. Disturbances in lipid metabolism (increased triglycerides or LDL-cholesterol levels) and an increase in inflammatory and fibrinolytic markers (high levels of homocysteine and fibrinogen). Significantly more pronounced metabolic deviations are observed in children with severe GH deficiency (defined as peak GH level below 5 ng/mL). GH deficiency may be accompanied by reduced bone mineral density compared to healthy or GH-treated children. Multiple hormonal deficiencies may develop in some patients with GH deficiency, such as additional deficiencies of thyroid hormones, gonadotropins and adrenocorticotropic hormone. As a result, there is additional impairment to the growth and the reproductive system of the children and the adolescents, as well as an increased risk of morbidity and mortality.

GH deficit also leads to significant impairment in patients' quality of life, including physical, social and emotional burdens, development of behavioral disorders and generalized anxiety. Parents also experience an emotional burden caused by their children's illness.

Somatrogon is a glycoprotein consisting of the amino acid sequence of hGH with one copy of the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin (hCG) at the N-terminal end and two copies of CTP (in tandem) at the C-terminal end. Glycosylation and CTP domains account for the longer half-life of somatrogon, which allows for weekly administration.

Epidemiological Data

The incidence of GH deficiency ranges from approximately 1:4,000 to 1:10,000 in the general population according to data from studies conducted in the United States, Europe, and Asia. In Europe, a study in Belgium put its prevalence at 1 in 5,600 in 2001, and an older observation from Denmark reported 2.15 in 100,000 (for the period 1980 to 1999). GH deficiency occurs more often in boys than in girls. For Bulgaria - according to National Health Insurance Fund, the average number of patients per month on GH therapy is 266. The trend for the period 2017 - 2022 is an increase in the number of patients needing therapy with GH, with 12-14% on an annual basis.

Efficacy data

The effectiveness and safety of somatrogon were evaluated in several clinical trials, but the analysis was based on data from the pivotal phase 3 registrational trial only.

Trial CP-4-006 is a phase 3, unblinded, randomized, active-controlled, parallel-group trial to evaluate the efficacy and safety of once-weekly somatrogon versus once-daily Genotropin in GH-treated children with GH deficit, for a period of 12 months, with an additional long-term, open-label extension in eligible patients. The aim of the trial is to establish the annual height dynamics - the height velocity (HV) achieved with the application of somatrogon once a week for a period of 12 months, as non-inferiority compared to once-daily Genotropin in children. The trial also investigated other parameters of growth, such as changes in bone maturation, safety and tolerability, and effect on quality of life (QoL). A total of 228 participants were randomized in a 1:1 ratio. The analysis included 135 patients, 67 in the somatrogon arm and 68 in the Genotropin arm. Results were comparable to those in the general population, with somatrogon demonstrating non-inferiority to Genotropin in patients with stimulated secretion of GH<6.7 ng/mL. LSM value of HV at month 12 favored somatrogon with a difference of 0.34 cm/year (10.11 cm/year for somatrogon vs. 9.77 cm/year for Genotropin). Mean SDS changes for height favored somatrogon over Genotropin at 6 (0.57 vs. 0.50) and 12 months (0.96 vs. 0.91), the increase in insulin-like growth factor-1 IGF-1 standard deviation score SDS of baseline characteristics at month 12 was higher in the somatrogon arm (+2.84 vs. +1.06). Similar changes were observed in bone maturation in both arms. The results of the secondary endpoints showed that the annualized HV at month 6

was comparable in both arms. Somatrogon was associated with a greater increase in baseline SDS for height at 6 and 12 months, a similar increase was seen with Genotropin. At month 12, bone maturation (ratio of bone age to chronological age) was below 1 in both arms (0.72), suggesting that the increase in bone age did not exceed patients' chronological age, with changes at month 12 being similar in both shoulders. Biochemical results showed an increase in absolute IGF-1 values in all patients during the 12-month treatment period. Over 95% of patients achieved mean IGF-1 SDS values within the reference range of ±2 SDS. One month after baseline, mean IGF-1 SDS reached 0 and remained >0 for 12 months (0.65 SDS at month 12) in the somatrogon arm, while in the Genotropin arm values remained near 0 SDS between month 1 and 12 (from −0.69 to −0.16 SDS). An interim analysis was conducted after the 12-month follow-up period of the main trial, covering mean HV, height SDS, bone maturation and biochemical markers, comparing those who continued on somatrogon follow-up and those who switched from Genotropin to somatrogon. The mean change from baseline (SD) in height SDS at month 12 was 0.42 (0.33) for the somatrogon/somatrogon arm and 0.49 (0.33) for the Genotropin/somatrogon arm.

Other more important clinical trials are the CP phase 3 **CP-4-009** and the CP phase 3 evaluation of therapy severity (**C0311002**).

CP-4-009 is a 12-month, randomized, open-label phase 3 clinical trial evaluating the efficacy and safety of once-weekly somatrogon compared with once-daily Genotropin in children with GH deficiency conducted in Japan. Results from the clinical trial CP-4-009 showed that children treated with somatrogon once weekly achieved comparable growth to those treated with Genotropin once daily, with a higher HV for somatrogon versus Genotropin. Other parameters such as changes in height SDS were also higher for somatrogon than Genotropin with comparable changes in bone maturation. Once-weekly somatrogon is better tolerated and has a similar safety profile to once-daily Genotropin. **C0311002** is a 24-week, open-label, randomized, cross-over, phase 3 clinical trial to assess sensation in relation to the severity of the therapeutic regimen of once-weekly somatrogon compared with once-daily Genotropin in children with GH deficiency on continuous GH therapy and from their parents. After a 24-week period, treatment with once-weekly somatrogon was associated with a significant reduction in treatment burden, based on the overall mean Life Interference total score compared to once-daily Genotropin (8.63 vs. 24.13, respectively mean treatment difference: −15.49). The percentage of children and parents reporting a reduction in weight from the therapy was significantly higher during the period of treatment with somatrogon - 47.4%, compared to Genotropin - 16.7%.

Safety data

Commonly reported adverse reactions following somatrogon treatment were injection site reactions (25.1%), headache (10.7%) and pyrexia (10.2%).

Data on comparators

Human growth hormone (somatropin) obtained by recombinant DNA technology, administered subcutaneously once a day, is currently the main method of treating growth hormone deficiency in children and adolescents. In Bulgaria, the authorized comparative alternatives to somatrogon, which are reimbursed by the NHIF, are Genotropin and Omnitrope.

Pharmacoeconomic indicators

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

Four positive assessments from HTA agencies of other countries G-BA (Germany), NICE (Great Britain), HAS (France), TLV (Sweden) are presented.

Applied analysis

A pharmacoeconomic cost-effectiveness analysis of Somatrogon versus available GH therapies (available once-daily GH versus once-weekly GH) in children with growth hormone deficiency was conducted. The perspective is of the paying institution - NHIF. The time horizon corresponds to the achievement of bone maturity - approximately 18-19 years of age of the patients. Costs and results are discounted by 3.5% per year. Modeling involves a Markov cohort model with a 1-year cycle length. The model tracks patients in two states: 'alive with treatment' and 'alive without treatment'. The results show that once-weekly somatrogon over a 12-month period versus once-daily Genotropin in children is the dominant technology. Due to the nature of the disease, no difference in life years added was observed, but a difference in life years with normal height and height gain was observed in favor of Ngenla treatment. The value of ICER (incremental cost-effectiveness ratio) for a year of life with normal height is below the cost-effectiveness threshold of BGN 60,636 (3 times GDP/capita), therefore Ngenla therapy is cost-effective for the Bulgarian healthcare system. Since the two GH drug therapies once a day and Ngenla once a week have comparable efficacy results, an adequate cost-effectiveness assessment is primarily based on a cost-minimum analysis. The cost-minimum results show an incremental increase in the cost of therapy per patient per year with Ngenla treatment.

Subgroup analyses
No subgroup analyzes were performed.

Costs for the assessed health technology
Only direct costs are presented - for the evaluated health technology Ngenla and the comparative alternative - Genotropin.

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. Two scenarios are considered: "A world without Ngenla" and "A world of Ngenla". The estimated number of patients treated with Ngenla 20 mg/ml - 1.2 ml solution for injection x 1 pre-filled pen in the first year is 70 and reaches 150 patients in the fifth year. The estimated number of patients treated with Ngenla 50 mg/ml - 1.2 ml solution for injection x 1 pre-filled pen in the first year is 50 and reaches 115 patients in the fifth year. The budget impact results show an increase in costs to the paying institution over the five-year period of analysis, excluding risk-sharing agreements and patient access schemes.

Conclusion

The new health technology Somatrogon has orphan medicinal product status. Somatrogon once weekly demonstrates a significant facilitation of treatment for the patient and the caregiver, offering greater convenience, a clearer intention to adhere to therapy, as well as a higher level of patient preference. Once-weekly somatrogon versus once-daily Genotropin in children is the dominant technology. Ngenla therapy is cost-effective for the Bulgarian healthcare system, as the value of the incremental ratio is below the break-even point. The results of the budget impact show an increase in costs for the paying institution.