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

HEALTH TECHNOLOGY ASSESSMENT

Toujeo

300 IU/ml – 1.5 ml solution for injection x 5 pre-filled pens

Insulin glargine

Therapeutic indication(s)	Treatment of insulin-dependent diabetes mellitus in individuals aged between 6 and 18 years.
Start/end date of procedure	22.05.2020 – 28.09.2020
Final decision	To add a 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 Toujeo

Health problem

Diabetes mellitus (DM) is a severe chronic disease of considerable social significance, determined by the growing number of patients, the need for timely diagnosis of the specific disease subtype, targeted treatment, training and control/self-control. Maintaining optimal glycemic control is the primary means for prevention of its severe complications, occurring after a certain period, especially in case of prolonged unsatisfactory control. For children and adolescents aged 0 to 18 years, the most common subtype - over 90% - is type 1 diabetes. It is based on genetic predisposition to autoimmune processes, in this case at the level of pancreatic B cells, producing insulin. The diagnosis of the disease is ascertained by confirming autoantibodies targeting pancreatic B cells.

Insulin treatment is mandatory and life-preserving for type 1 diabetes, comprising over 90% of the child and adolescent patient population. In this sense, Toujeo insulin is considered the most suitable option for the treatment of type 1 diabetes.

Much less frequent in children and adolescents is type 2 diabetes, due to insulin insensitivity, 80% of which is associated with overweight or obesity. In some patients with type 2 diabetes the diagnosis is made at the time of already developed diabetic ketoacidosis (DKA) and treatment is also initiated with insulin.

In the course of type 1 diabetes there are several stages and phases:

- The first stage of diabetes is defined as a condition in which 2 or more autoantibodies are present, but without any signs of the disease.
- The second stage - again without clinical signs, but with evidence of already increased blood glucose in the range of impaired glucose tolerance.
- The third stage is diagnosed overt diabetes.
- The fourth stage is continuing type 1 diabetes with a chronic need for lifelong insulin treatment.

With unsatisfactory metabolic control, complications occur within 5 - 10 years after its diagnosis. Overall, increased mortality is observed in patients with type 1 DM, diagnosed in childhood and adolescence. The main goal for all patients with type 1 diabetes is to receive the best possible treatment, training and motivation for self-control and support.

Toujeo (Insilin Glargine 300 IU/ml or GLA-300) is used in patients aged between 6 and 18 years with type 1 diabetes.

Toujeo (Insilin Glargine 300 IU/ml or GLA-300) is a second generation long-acting insulin analogue. Toujeo (Insulin Glargine 300) is intended for subcutaneous use only, has a prolonged effect lasting up to 30 - 36 hours and with a minimal peak. These two advantages make it a more preferred basal insulin compared to Glargine 100, with a lower risk of hypoglycaemia and a need for a single injection daily.

Epidemiological data

Data from two epidemiological studies show a much lower annual average morbidity for Bulgaria - 8.4 to 9.3/100,000 child population, compared to other countries, where the incidence varies from 21.5 to 35.3/100,000 child population. According to the Bulgarian National Association of Pediatric Endocrinology, the number of patients under the age of 18 with type 1 diabetes is about 1600 - 1800.

Efficacy data

The therapeutic efficacy and safety profile of GLA-300 were analyzed in a pediatric clinical trial: **EFC13957 (EDITION JUNIOR)** (NCT02735044) to evaluate the efficacy of a more concentrated form of insulin glargine (GLA-300) versus GLA-100 as regards the change in glycated hemoglobin A1 (HbA1c) from the beginning to the end point (month 6/week 26) in children and adolescents with diabetes mellitus 1.

The study achieved its main goal – non-inferiority of GLA-300 compared to GLA-100, demonstrated by the change in HbA1c from baseline through week 26. The effect of GLA-300 on HbA1c change during 12-month treatment was comparable to GLA-100 in children and adolescents (aged 6–17 years) with DM 1.

Secondary efficacy endpoints included a change in fasting plasma glucose (FPG), mean plasma glucose (8-point SMPG profiles).

The change in FPG over time from baseline to week 52 is small and similar in both treatment groups. No significant difference in FPG was observed between the therapeutic groups from the beginning through week 52. The percentage of patients that reached the pre-determined target for FPG (≤130 mg/dL [7.2 mmol/L]) at week 26 and those with no episode of severe and/or documented hypoglycaemia (SMPG ≤ 54 mg/dL [3.0 mmol/L]) in the last 3 months of the main 6-month randomized period was similar in both therapeutic groups. Based on 8-point SMPG profiles, the baseline mean plasma glucose values were similar in both treatment groups (GLA-300: 189.48 mg/dL [10.52 mmol/L]; GLA-100:194.47 mg/dL [10.79 mmol/L]). The average 24-hour plasma glucose remained stable at week 26 in both treatment groups (GLA-300: 193.96) mg/dL [10.77 mmol/L]; GLA-100: 187.85 mg/dL [[10.43 mmol/ L]). The reduction of the average plasma glucose from baseline through week 26, based on 8-point

SMPG profiles is similar across treatment groups (GLA-300: 4.48 mg/dL [0.25 mmol/L]; GLA-100: -6.62 mg/dL [-0.37 mmol/L]).

Meta-analyses
A qualitative comparison has been performed of the efficacy and safety data of GLA-300 for different populations of patients included in GLA-300 clinical development program. The assessed efficacy endpoints are HbA1c and FPG.

Data on HbA1c and FPG in the four studies show a similar response to treatment with GLA-300 in patients with DM 1 and DM 2.

Data from GLA-300 clinical trials in individually titrated adult patients with DM 1 and DM 2 - EFC12456, EFC11628 and EFC12347, as well as in children with DM1 show good efficacy in terms of glycemic control, demonstrated by the decrease in mean HbA1c and mean FPG with respect to the initial values. The decrease in HbA1c and FPG is similar and follows a similar pattern in adults and children. These results support the hypothesis that GLA-300 is effective also in children with diabetes 2.

The estimated efficacy parameters are consistent in patient populations and various subgroups for characteristics, considered particularly important for pediatric diabetes mellitus 2 population. The degree of improvement is similar in adults and children with DM 1, but is more pronounced in patients with DM 2, and as expected, specifically in patients with DM 2, started on insulin therapy. Overall, the available efficacy data for GLA-300 are considered to be applicable to the pediatric DM 2 population.

Safety data

The most commonly reported adverse reactions include hypoglycaemia, lipohypertrophy and injection site reaction.

Data on comparators

Toujeo alternatives are the rest of the long-acting insulin analogues - Lantus (glargine 100), Levemir (detemir) and Tresiba (degludec). Toujeo has advantages over Glargine 100, as well as Levemir, due to its longer lasting effect and peakless initial effect. These advantages make it safer as concerns initial hypoglycemia (minimal peak of action), and its single application (over 24 hours effect) satisfies patients to a greater extent.

Pharmacoeconomic indicators

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

No data have been found on the health technology assessment by government institutions of UK, France, Germany and Sweden regarding Toujeo (insulin glargine 300) for treatment of type 1 diabetes mellitus in adolescents and children over 6 years of age.

Applied analysis

A cost-minimisation pharmacoeconomic analysis was performed based on the evidence of similar therapeutic outcomes - effectiveness, similar therapeutic efficacy and safety profile based on a clinical trial (EDITION JUNIOR) (NCT 02735044), which directly compares insulin glargine 100 and insulin glargine 300. The perspective of the analysis is that of the paying institution - NHIF, the selected time horizon is one year. Given the length of the time horizon and the type of analysis, discounting and modeling are not applied.

Comparators are consistent with those used in the clinical trials and which are most likely to be replaced by the new technology - insulin glargine 100 IU, insulin detemir and insulin degludec.

The costs of short/rapid-acting insulin to cover prandial insulin needs are the same for all comparators and are not included in the analysis.
No sensitivity analysis was applied.

The results of the cost-minimisation analysis show that with Glargine 100 (Lantus, Abasaglar) and Glargine 300 (Toujeo) therapies, there is no difference in the annual cost of treatment.
Subgroup analysis is not applied.

Costs of the assessed health technology

Only direct costs are presented - of the assessed therapy and alternatives in line with the dosage and method of administration.

Budget impact analysis

The budget impact analysis has the perspective of the National Health Insurance Fund with a time horizon 5 years. The target population of the present analysis includes pediatric patients aged ≥ 6 years diagnosed with diabetes mellitus, and in particular diabetes mellitus type 1 in Bulgaria. The estimated number of patients in the first year is 119, expected to reach 497 in the fifth year.

A sensitivity analysis is applied, according to which the three principal factors influencing the budget impact are: number of patients for a period of five years, average cost of therapy with alternatives, and the cost of Toujeo therapy (insulin glargine 300).

The inclusion of the health technology in the PDL will lead to per annum cost savings, without taking into account risk - sharing agreements and patient access schemes.

Conclusion

GLA-300 has similar efficacy (non-inferiority) compared to GLA-100 in terms of the effect of reducing HbA1c, baseline fasting glucose and the dynamics of glycemia during the 8-fold blood glucose profile. As regards the safety, there was no statistically significant difference in the overall incidence of hypoglycaemic events between the two medicinal products being compared. The results of the cost-minimisation pharmacoeconomic analysis show equal costs for the use of both products – insulin glargine 100 and insulin glargine 300. The budget impact analysis shows that Toujeo reimbursement for the new patient population leads to cost savings for the paying institution for a 5-year period.