INSULIN GLARGINE IS COST-EFFECTIVE IN TREATMENT OF PATIENTS WITH DIABETES TYPE-2 IN WHOM NPH INSULIN DOES NOT PROVIDE ADEQUATE GLYCAEMIC CONTROL – THE CASE OF POLAND

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Background

Diabetes mellitus is one of the most prevalent diseases in Poland. Type 2 diabetes mellitus (T2DM), with the overall prevalence of 1.6-3.7% and the incidence rate of around 200 cases per 100,000 person per year, contributes to 90% of all diabetic cases.

T2DM is a progressive disease leading to many serious and even fatal complications when improperly controlled. Early complications occur as a result of severe glucose fluctuations and include ketoacidosis, coma, hyperglycaemic hyperosmolar syndrome, lactic acidosis, and hypoglycaemia. Late complications are a consequence of prolonged hyperglycaemia and include variety of conditions classified as microangiopathies (e.g. retinopathy, nephropathy, and neuropathy) and macroangiopathies (e.g. ischemic heart disease, stroke, limb ischemia, and hypertension).

According to estimates, the mortality rate attributable to T2DM reaches 15 deaths per 100,000 per year, however in 70% of cases diabetes-associated cardiovascular complications are diagnosed as direct cause of death.

T2DM is a progressive condition, which requires treatment intensification during the course of disease. The patient should achieve the lowest possible HbA1c level without a significant increase in the frequency of hypoglycaemia and reduction of the patient's quality of life.

Objective

The aim of this analysis was to compare costs and effectiveness of insulin glargine (Lantus®) in the treatment of diabetes mellitus type 2 (T2DM) in patients whose glycaemic control cannot be maintained using protamine Hagedorn insulin (NPH) and to determine whether it is cost-effective option for T2DM patients in Poland.

Population

As recommended by NICE and SIGN, the insulin therapy should be preferably initiated with NPH, while the use of long-acting insulin, including insulin glargine, is restricted to patients with specific clinical conditions, such as those without adequate glycaemic control or subjects experiencing symptomatic hypoglycaemia. These criteria were adopted in many European countries for reimbursement of LANTUS. The reimbursement restrictions are clinically and economically justified as LANTUS is both more effective and more expensive than NPH. Limiting the reimbursement population preserves the most effective therapy for those patients who would gain most from its use while maintaining fiscal discipline.

With regards to those arguments, the population in the analysis was restricted to patients who had failed the NPH-based insulin therapy. The target population was defined as the patients with T2DM treated with NPH for ≥6 months with:

- inadequate glycaemic control (HbA1c ≥ 8%) and/or
- experiencing ≥ 1 episode of severe or nocturnal hypoglycaemia reporting at this time.

Methods

The analysis was performed with the use of CORE diabetes model. This is a well-validated and widely used application dedicated to perform interactive analysis (www.corediabetes.com) related to diabetes. The tool was designed to compare long-term health and economical outcomes of various diabetes treatment (both for diabetes type 1 and 2). CORE diabetes model is constantly updated to meet the most recent clinical data.

There is a wide range of parameters of the CORE model that can be adjusted in accordance with the assumptions of the analysis performed. The range of parameters that were implemented in the model for the analysis presented include the following elements:

- clinical effectiveness and safety (parameters based on observational studies);
- patients characteristics (parameters based on RCT studies in T2DM and polish epidemiological data);
- utilities related to diabetes and diabetes complications;
- cost of insulin therapy, diabetes management and complications.

A lifetime horizon was adopted to recognize the full picture of long-term outcomes in T2DM. Clinical outcomes were discounted at 3.5% and costs were discounted with at 5% which is consistent with guidelines of polish HTA agency.

The main outcome measures used in the economic analysis were costs of treatment and quality adjusted life years (QALYs). Incremental cost utility ratios (ICUR) were calculated and compared to defined polish cost-acceptability threshold (25,800 EUR/ QALY). In the probabilistic sensitivity analysis (PSA) the likelihood of IGlar being cost-effective was calculated.

Data

Efficacy and safety

A systematic literature review of clinical studies was conducted in order to evaluate the effectiveness and safety of insulin glargine in T2DM. No randomized control trials were found for subpopulations of patients who failed NPH-based treatment. Due to lack of appropriate data from RCTs the non-randomized clinical data were used as the source for the analysis. These are so far the best available evidence.

Population from the nRCT studies was to a large extent convergent with the definition of target population. However only in comparison with NPH it was possible to obtain the relative effectiveness of IGlar and its comparator. The mean baseline Hba1c in these studies was >8% which corresponds to the defined reimbursement criteria.

The summary of the characteristics of studies used in analysis is presented in the table below (Table 1).

Table 1. Summary of studies characteristics – IGlar vs NPH in population who failed NPH treatment

Study	Methodology	Number of patients	Age [years]	BMI [kg/m2]	HbA1c [%]	Concomitant treatment	Observation interval [months]
LAUREL	Retrospective	796 vs 396	57.9 vs 60,8	NA	9.0 vs 9.1	OAD/bolus	4-9
LAURUS	Retrospective	5329 vs 2395	58.8 vs 60.5	29.6 vs 29.7	8.9 vs 9.0	OAD	3

The following parameters were included in the model: HbA1c change, BMI change, hypoglycaemia frequency. Those are some of the most important indicators of therapeutic efficacy in diabetes, the range of effects selected was also defined in accordance with the adopted modelling strategy (i.e. CORE model application). The clinical effects applied in calculations are stated in Table 2.

Table 2. Efficacy and safety parameters - summary

Intervention	LAUREL					LAURUS				
	HbA1c change [%], mean (SE)	BMI change [kg/m^2]	hypoglycaemia frequency (per 100 patient-years)			HbA1c change [%], mean (SE)	BMI change [kg/m^2]	hypoglycaemia frequency (per 100 patient-years)		
			Overall	Major	Minor			Overall	Major	Minor
IGlar	-1.8 (0.05)	0	600	12	588	-1.7 (0.02)	0	NA, Assumed as in LAUREL: 600	0	600
NPH	-0.7 (0.06) Min: -0.6; Max: -0.8	0	2040	48	1992	-0.6 (0.05) Min: -0.5; Max: -0.7	0	NA, Assumed as in LAUREL: 2040	36	2004

Costs

Costs were estimated from public payer's (National Health Fund, NHF), and NHF + patients' perspective. Only the NHF + patients' perspective is analysed within this publication. All the values were established according to the most recent Polish costs and legal regulations data. It was assumed that 1 EUR = 4.10 PLN.

Insulin therapy

Insulin dosage and percentages of patients in particular treatment schemes (bolus insulin or OAD) were established according to data from studies included in clinical effectiveness analysis. It was assumed that the applied algorithms are only one-line treatments i.e. no switch is allowed.

Table 3. Cost of insulin therapy

Algorithm	Daily insulin dose		Cost per year [€]			
	Basal [IU]	Bolus [IU]	Basal	Bolus	OAD [a]	Total
IGlar + OAD/bolus	27.9	42.3	373	307	90	541
NPH + OAD/bolus	31.4	41.3	196	300	90	377
IGlar + OAD	27.9	-	373	-	90	463
NPH + OAD	28.8	-	179	-	90	269

a) 2000 mg of metformin and 2 mg of glimepiride a day

Diabetes management and complications

Health states that were assigned the relevant costs include: myocardial infarction, angina, congestive heart failure, stroke, peripheral vascular disease, end-stage renal disease (kidney transplantation, haemodialysis, peritoneal dialysis), major hypoglycaemia, amputation, gangrene, ulcers, loss of vision, laser therapy, cataract surgery, severe and others. The values for the main complications are presented in Table 4.

Table 4. Cost of diabetes complications

Health state	Cost in the first year [€]	Cost in the following years [€]
Myocardial infarction	3,030	668
Angina	203	203
Heart failure	1620	801
Stroke	2256	27
Kidney transplantation	15,300	4033
Haemodialysis	17,687	16,886
Peritoneal dialysis	21,477	20,676
Neuropathy	161	91

Utility values

Utility values were identified by means of a systematic review of published data related to diabetes modelling and diabetes-related quality of life. The detailed analysis of the data found was performed in order to estimate the most reliable utility parameters. The set of utilities was very similar to that obtained from a systematic review by IMS, presented on ISPOR 15th Annual European Congress.

Results

IGlar + OAD scheme

According to data from nRCT study LAURUS IGlar + OAD is more effective than NPH + OAD. The obtained difference in QALY is 0.792. The life-time cost of treatment with IGlar + OAD (including costs of diabetes management and complications) was estimated to be 9900 €. It is 1592 € more than the cost of NPH+OAD.

IGlar + OAD scheme was found to be highly cost-effective. The estimated cost per QALY gained is 2010€ which is far below the defined cost-acceptability threshold (25,800 €/ QALY). The cost-effectiveness of IGlar + OAD was confirmed in the probability sensitive analysis as 100% of the 1000 simulations' results had fallen below the defined threshold.

Figure 1. Scatterplot IGlar + OAD vs NPH + OAD

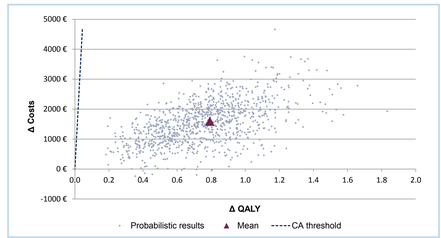

Table 5. Clinical results - T2DM (IGlar + OAD) – effectiveness from nRCT study LAUREL

Result	IGlar + OAD [$CI_{95\%}$]	NPH + OAD [$CI_{95\%}$]	Difference [$CI_{95\%}$]
QALY	6.146 [3.115; 8.110]	5.354 [2.764; 6.907]	0.792 [0.289; 1.327]
Insulin therapy[a] [€]	3956	2085	1871
Management and complications [€]	5944	6223	-279
Total costs [€]	9900 [5700; 14,288]	8308 [4902; 12,358]	1592 [276; 2993]
ICUR [€]	-	-	2010

a) includes OAD

IGlar +OAD/bolus scheme

According to data from nRCT study, IGlar + OAD/bolus is more effective than NPH + OAD/bolus. The obtained QALY difference is 0.695. The total life-time cost of treatment with IGlar + OAD-bolus was estimated to be 10,181 €. It is 1335 € more than the according cost of NPH + OAD/bolus.

IGlar + OAD/bolus scheme was found to be highly cost-effective in comparison with NPH + OAD/bolus. The estimated cost per QALY gained is 1950 € which is far below the defined cost-acceptability threshold (25,800 €/ QALY). The cost-effectiveness of IGlar + OAD/bolus was confirmed in the probability sensitive analysis as 100% of the 1000 simulations' results had fallen below the defined threshold.

Figure 2. Scatterplot IGlar + OAD/bolus vs NPH + OAD/bolus

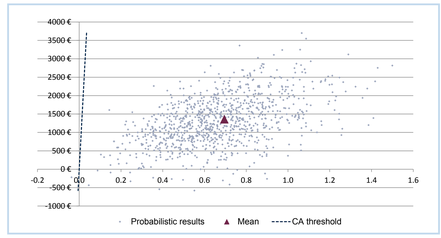

Table 6. Clinical results - T2DM (IGlar + OAD/bolus) – effectiveness from nRCT study LAUREL

Result	IGlar + OAD/bolus [$CI_{95\%}$]	NPH + OAD/bolus [$CI_{95\%}$]	Difference [$CI_{95\%}$]
QALY	6.007 [3.131; 7.946]	5.312 [2.801; 6.885]	0.695 [0.241; 1.194]
Insulin therapy[a] [€]	4547	2904	1642
Management and complications [€]	5634	5921	-287
Total costs [€]	10,181 [6053; 14,100]	8826 [5437; 12,649]	1355 [52; 2683]
ICUR [€]		-	1950

a) includes OAD

Conclusions

Insulin glargine was considered a highly cost-effective option for management of diabetes mellitus type 2 in patients who failed NPH-based treatment in comparison with continuation of NPH treatment. The higher price of insulin is counterbalanced by the decreased resource usage related to superior efficiency and better safety profile.

Bibliography

1. Jarek-Martynowa I, Shamkhalova M, Shestakova M. Glargine Utilization in Russia: A Retrospective Comparative Study To Evaluate Patients Switched from NPH Insulin to Insulin Glargine Compared with Patients Maintained on NPH. Diabetes. 2011; 60(Supplement_1):A608.
2. Shestakova M, Glinkina I. Insulin Glargine (GLAR) and NPH Insulin (NPH) in Real Life in Russia in Patients with Type 2 Diabetes (T2D). Insulin Glargine (GLAR) and NPH Insulin (NPH) in Real Life in Russia in Patients with Type 2 Diabetes (T2D). 2009.