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

HEALTH TECHNOLOGY ASSESSMENT

Suliqua

100 U/ml + 33 mcg/ml – 3 ml solution for injection x 3 pre-filled pens

100 U/ml + 50 mcg/ml – 3 ml solution for injection x 3 pre-filled pens

Insulin glargine/lixisenatide

Therapeutic indication(s)	Indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors.
Start/end date of procedure	10.02.2020 - 18.12.2020
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases, paid for by the NHIF and in Annex 2 of the PDL for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act.

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

Health problem

Diabetes mellitus (DM) is a chronic metabolic disease, characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. (WHO, 1999)

Classification of diabetes mellitus

1. Type 1 DM (DM1) – generally due to autoimmune beta-cell destruction leading to absolute insulin deficiency
2. Type 2 diabetes (DM2) - resulting from progressive insulin secretory defect against the background of insulin resistance
3. Gestational diabetes (GD) - diagnosed during pregnancy
4. Other specific types of diabetes

A. Genetic defect in beta-cell function
B. Genetic defect in insulin action
C. Diseases of the exocrine pancreas
D. Endocrinopathies
E. Effects of drugs or chemicals
E. Infections
G. Other genetic syndromes associated with diabetes

Type 1 diabetes is usually associated with autoimmune-related (antibodies present) loss of beta cells and subsequent absolute insulin deficiency, a weak element of heredity, normal or reduced body weight. It manifests itself in children and adolescents with typical acute disease symptoms (polydipsia, polyuria, polyphagia, but with weight loss, astheno-adynamia, etc.) and with significantly increased blood sugar level - very often as overt ketoacidosis.

DM2 has a different clinical feature than DM1 – usually begins after the age of 40 (but with a tendency to shift to younger age), ketoacidosis occurs rarely, usually has discrete signs at diagnosis, has no association with the HLA system, no present autoantibodies, in over 30% of cases there is a positive family history.

Unlike DM1, DM2 has a long antecedent period prior to being diagnosed. A number of conditions are involved in the pathogenetic chain - genetic predisposition, environmental factors, contributing to its phenotypic expression, mutually potentiating themselves insulin resistance and increased weight, forming a vicious circle, obesity and metabolic syndrome, prediabetes (postprandial hyperglycemia is observed first, and later fasting hyperglycaemia, as inhibition of hepatic gluconeogenesis is disturbed), undiagnosed diabetes mellitus and

usually only after 5-10 years the diagnosis is made, most frequently due to a manifestation of a diabetic complication and/or an acute condition that increases the need for insulin, which the pancreas can no longer respond to adequately. The realization of macrovascular (cardiovascular) diabetic complications begins at the stage of insulin resistance and hyperinsulinemia, and of microvascular - when the rise in glycemia begins.

Diabetes mellitus is a chronic disease characterized by both acute and progressively developing macro- and microvascular complications. It is the chronic complications that define disability, the reduced duration and quality of life, unfavorable prognosis and the leading share of financial costs. Diabetic complications begin asymptomatically for the patient and can be detected as early as the diagnosis of DM2 or even in the pre-diabetic stage (micro- and macrovascular) and in the presence of insulin resistance (macrovascular).

When diagnosing DM2, the lifestyle should be reassessed and it should be changed accordingly by patient education, regular self-control, determination of targeted blood sugar levels, diet, physical activity, restriction in alcohol consumption, smoking cessation.

Treatment with oral and injectable non-insulin hypoglycaemic agents in DM2

- Indications - drug treatment is started when training/an adequate change in lifestyle has already been made; HbA1c > 7.0%, venous fasting plasma glucose > 6.1 mmol/l;

- Groups of drugs used: Biguanides (metformin); Insulin secretagogues (Sulfonylureas, Meglitinides); Thiazolidinediones (pioglitazone); Alpha-glucosidase inhibitors; DPP-4 - inhibitors (sitagliptin, vildagliptin, linagliptin, saxagliptin) GLP-1 receptor agonists - GLP-1 mimetics (exenatide, exenatide LAR, lixisenatide) and GLP-1 analogues (liraglutide, dulaglutide, semaglutide); SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin)

II. Insulin treatment

Indications for insulin treatment in diabetes mellitus: inability to achieve good glycemic control despite the maximum doses of combinations of oral and injectable non-insulin hypoglycaemic preparations; contraindications or hypersensitivity to oral and injectable non-insulin antidiabetics; decompensation associated with intercurrent illness; treatment in the perioperative period; pregnancy and lactation; critically ill patients. Treatment with insulin is added when HbA1c rises > 7.0%.

Suliqua is a fixed combination of insulin glargine and the glucagon-like peptide-1 receptor agonist lixisenatide. The medicinal product is indicated for the treatment of adult patients with

insufficiently controlled type 2 diabetes mellitus 2 to improve glycemic control in addition to diet and exercise in addition to metformin with or without SGLT-2 inhibitors.

Epidemiological data

Type 2 diabetes has reached the size of a pandemic. For the last 20 years alone, the number of people with diabetes in the world has increased 3 times and in 2019 they are about 438 million, expected to become 700 million by 2045.

IDF data from 2019 for Bulgaria show that 8.3% of the population aged 20 to 79 years old have diabetes, which given the population of about 7 million Bulgarians according to the National statistical institute from 2019, means that about half a million people have diabetes. The mortality rate related to diabetes in Bulgaria for 2019 is 6,287 in the age group 20-79.

Efficacy data

In order to evaluate the therapeutic efficacy and safety profile of insulin glargine/lixisenatide (iGlarLixi), indicated for the treatment of adult patients with T2DM, the results of two clinical trials were analyzed.

Abbreviations used: T2DM - type 2 diabetes mellitus; iGlarLixi - insulin glargine / lixisenatide; OAD - oral antidiabetic drug; HbA1c - glycated hemoglobin; CI - confidence interval; SMPG - self-measured plasma glucose; LS - by the method of least squares; SE - standard error; FPG - fasting plasma glucose

1. LixiLan-O clinical trial comparing efficacy and safety of iGlarLixi versus insulin glargine and lixisenatide with background treatment with metformin.

- *Study design and dose regimen* – a randomized, 30 weeks, active controlled, open, multicenter, multinational study with 3 parallel groups.
- *Results*: Change in HbA1c - Mean (LS) difference (SE) versus insulin glargine: -0.29 (0.048), Mean (LS) difference (SE) versus lixisenatide: -0.78 (0.059); Proportion of patients with HbA1c response <7.0% at week 30,% - Difference (95% CI) versus insulin glargine: 14.31% (8.37% to 20.25%), Difference (95% CI) versus lixisenatide: 40.61% (33.63% to 47.59%); Proportion of patients with HbA1c response ≤6.5% at week 30 - Difference (95% CI) vs insulin glargine: 16.35% (10.13% to 22.58%), Difference (95% CI) versus lixisenatide: 36.38% (29.81% to 42.95%); Changes in plasma glucose level at 2 hours, mg/dL - Mean (LS) difference (SE) vs insulin glargine: -38.44 (3.341), Mean (LS) difference (SE) relative to lixisenatide: -16.44 (4.261); Change in body weight, kg - Mean (LS) difference (SE) vs insulin glargine: -1.40 (0.250), Mean (LS) difference (SE) relative to lixisenatide: 2.01 (0.307); Change in FPG, mg/dL - Mean (LS) difference (SE) vs insulin glargine: -3.45 (2.103), Mean (LS) difference (SE) vs lixisenatide: -35.38 (2,589); Change in the daily average of the

7-point profile of SMPG - Statistically Larger Reduction in iGlarLixi in comparison with insulin glargine or lixisenatide; Proportion of patients with HbA1c response <7.0%, no weight gain and no documented hypoglycaemia, % - Difference (95% CI) versus insulin glargine: 12.98%, Difference (95% CI) versus lixisenatide: 5.61%

2. **LixiLan-L clinical trial,** comparing the efficacy and safety of iGlarLixi versus insulin glargine, with or without metformin.

- Study design and dose regimen – a randomized, 30 weeks, active controlled, open, multinational, multicenter study with two parallel groups.
- Results: Change in HbA1c - Mean (LS) change (SE) relative to insulin glargine: -0.52 (0.60); Proportion of patients with HbA1c response <7.0% at week 30,% - Difference (95% CI) vs insulin glargine: 25.52%; Proportion of patients with HbA1c ≤6.5% at week 30 - Difference (95% CI) vs insulin glargine: 19.76%; Changes in Plasma glucose level at 2 hours, mg/dL - Mean (LS) difference (SE) relative to insulin glargine: -61.82 (4,521); Change in body weight, kg – Average (LS) difference (SE) from insulin glargine: -1.37; Change in FPG, mg/dL – Mean (LS) difference (SE) versus insulin glargine: -3.45 (2.103), Mean (LS) difference (SE) relative to lixisenatide: -35.38 (2,589); Change in daily average of 7-SMPG point profile - Statistically significant greater reduction at iGlarLixi compared to insulin glargine. Proportion of patients with HbA1c response <7.0%, no weight gain and no documented hypoglycaemia, % - Difference (95% CI) relative to insulin glargine: 10.94%.

In order to evaluate the comparative efficacy and safety of iGlarLixi versus comparators, the following have been conducted:

- network meta-analysis (NMA),
- indirect comparison (ITC) and
- summary analysis of individual patient data.

Due to the limitations of the NMA and the heterogeneity of the composite analysis with individual data, ITC is accepted as the most appropriate assessment approach. At ITC the iGlarLixi's comparison is with the following comparators: Basal insulin (long - acting insulin insulin and intermediate-acting insulin); Basal insulin + short-acting or fast-acting insulin; Premixed insulin; Glucagon-like peptide-1 receptor agonists (GLP-1 RA); Dipeptidyl peptidase-4 (DDP-4) inhibitors; Sodium glucose cotransporter 2 -2 inhibitors (SGLT-2); Oral antidiabetic medicinal products (OAD).

Safety data

Summary of the safety profile

The most commonly reported adverse reactions during treatment with iGlarLixi are hypoglycaemia and gastrointestinal adverse reactions.

Combined safety data from LixiLan-O and LixiLan-L

The proportion of patients with at least 1 TEAE (Treatment emergent adverse events) is similar in the groups (55.4% for iGlarLixi and 50.2% for insulin glargine). The proportion of patients with severe TEAE was also similar (4.6% with iGlarLixi and 4.4% with insulin glargine). TEAE leading to definitive cessation of treatment were found in 22 patients (2.6%) in the iGlarLixi group (pooled data) and 12 (1.4%) in the insulin glargine group; the proportion was higher in the lixisenatide group (9.0%). In 9 patients TEAE leads to death (3 patients [0.4%] in the iGlarLixi group, 5 patients [0.6%] in the insulin glargine group and 1 patient [0.4%] in the lixisenatide group). In 7 of these 9 patients death occured during the treatment period, in 2 after the treatment period (1 in the iGLarLixi group and 1 in the insulin glargine group).

Data on comparators

The available therapeutic alternatives in Bulgaria are:

- Xultophy (insulin degludec/liraglutide)
- Basal human insulins (NPH) and insulin analogues in combination with GLP-1 RA: lixisenatide; exenatide; liraglutide; dulaglutide; semaglutide

Pharmacoeconomic indicators

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

The conclusions from the health technology assessment performed by the health institutions of Germany iQWIG, and Sweden's TLV have been described. Although both agencies give a positive assessment for inclusion of the medicinal product in their reimbursement lists, both state institutions note a lower efficiency and lower added benefits of the medicinal product. The evaluation of iQWIG notes that overall the medicinal product has no added benefits and the likelihood of added benefits pertains to only certain groups of patients.

Applied analysis

The aim is to evaluate the cost-effectiveness of Suliqua in patients with DM2 for improving glycemic control in combination with metformin when metformin alone or in combination with another oral glucose-lowering drug product or with basal insulin does not provide

adequate control. A cost-minimisation analysis is attached, which represents the Bulgarian therapeutic practice and standards of treatment. To prove equivalence, a network analysis is presented that compares the product Suliqua with the nearest alternatives – a combined product Xultophy (insulin degludec/liraglutide) + 1 Oral Antidiabetic Drug (OAD), or a combination of monoproduct insulin + GLP-1 RA. The network analysis has not established a statistically significant difference, but clearly shows lower efficacy of Suliqua. The results are in favour of the compared alternatives.

Costs of the assessed health technology

Costs of treatment with Suliqua and alternatives are presented. The main comparators are either the combined product Xultophy or monoproducts insulin + GLP 1 receptor agonist.

Budget impact analysis

The analysis of the budget impact was conducted by presenting the main comparators, based on a pharmacotherapeutic guide to endocrinology and metabolic diseases - namely Xultophy, as the only alternative fixed combination; a combination of basal insulin and OAD, from the group of GLP-1 receptor agonists. Given the lower cost of the product, the introduction of the new technology is expected to have a negative effect on the budget in all scenarios considered, not taking into account risk - sharing agreements and for patient access schemes.

Conclusion

The advantages of the new health technology should be considered at several levels:

1. Advantages of its components as representatives of the described new therapeutic groups (GLP-1 RA and insulin analogues) compared to older therapeutic groups
2. Advantages of the combination over the individual use of its components.
3. Advantages over other similar combinations.

Suliqua is a fixed combination of insulin glargine and the glucagon-like peptide-1 receptor agonist lixisenatide. The fixed combination, proposed in one product provides different and synergistic mechanisms of action, ensuring a better balance between the glycemic control, the change in body weight and the hypoglycaemia compared with insulin. In patients with DM2 who have had inadequate control with oral antidiabetic drugs, the addition of insulin glargine/lixisenatide to metformin results in improvement in HbA1c and plasma levels fasting glucose, the 7-point profile of self-measured plasma glucose and body weight compared to the addition of insulin glargine alone. In patients with DM2, which are inadequately controlled with basal insulin, with or without metformin, insulin glargine/lixisenatide demonstrated efficacy with respect to the same parameters compared with the addition of insulin glargine alone. In addition, with insulin glargine/lixisenatide there are fewer gastrointestinal side

effects than lixisenatide. Also, the fixed insulin glargine/lixisenatide combination provides patients with not only an efficient but also a simple regimen, easy to titrate, with the possibility of good adherence to treatment.

Compared to therapeutic alternatives, the reviewed health technology Suliqua offers the unique possibility for reducing the adverse effect of being "fixed" and achieving a higher degree of individualization of treatment by administering two different ratios of insulin and GLP-1RA in different pens. The possibility to select the most appropriate therapeutic regimen with Suliqua represents an unquestionable advantage.

The results of the pharmacoeconomic analysis show that while having equal efficacy, the new health technology is associated with lower costs. In the budget impact analysis a reduction in the cost for the payer is set.