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

HEALTH TECHNOLOGY ASSESSMENT

Forxiga
5 mg film-coated tablet x 30
dapagliflozin

Therapeutic indication(s)	Indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.
Start/end date of procedure	06.02.2020 – 13.08.2020
Final decision	Inclusion in: - Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF); - Annex 2 of the PDL for purchase by medical establishments 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 Forxiga

Health problem

Diabetes mellitus (DM) is a socially important disease due to its widespread prevalence. DM is a metabolic disease characterized by hyperglycemia resulting from disturbances in insulin secretion, insulin action, or both. According to the current classification of DM, 4 types are distinguished - type 1 (DMT1) – resulting from beta-cell destruction, usually leading to absolute insulin deficiency; type 2 DM (DMT2) - resulting from progressive insulin secretory defect against the background of insulin resistance; *other specific types of diabetes* - due to other causes: genetic defect in beta-cell function, genetic defect in insulin action, diseases of the exocrine pancreas, exposure to drugs or other chemical compounds, other diseases; gestational diabetes mellitus (GDM) - a disorder of carbohydrate tolerance diagnosed during pregnancy.

Inadequate control of type 1 diabetes can cause serious complications leading to increased mortality, poor quality of life and high direct and indirect expenses.

Insulin deficiency can cause diabetic ketoacidosis (DKA), which is a severe acute complication, requiring emergency hospitalization and leading to a fatal outcome if no emergency measures are taken. Higher than required doses of insulin can cause another acute complication - *hypoglycaemia*, which is usually defined as blood glucose values ≤ 3.9 mmol/L. Hypoglycaemia is a major barrier to achieving good glycemic control. Very often hypoglycaemic events are not identified, especially if they occur at night. Severe hypoglycaemic crises can be life-threatening, and mild to moderate crises are associated with significant burden on patients and their relatives. Patients receiving intensive insulin therapy are at increased risk of developing hypoglycaemia.

Possible complications of DMT1 are insulin resistance, excessive weight or obesity, in the long run microvascular and macrovascular damage lead to complications such as hypertension, cardiovascular disease (CVD), cerebrovascular disease, retinopathy, nephropathy and neuropathy, which accounts for the increased mortality in patients with DMT1, that may be up to 4 times higher than in the general population.

Patients with DMT1 have a lower quality of life compared to the general population. The health-related quality of life is further aggravated by the presence of complications.

Therapeutic goals are directed at the prevention of complications and disability.

Forxiga (dapagliflozin) is the only SGLT2 inhibitor that is indicated in adults for the treatment of insufficiently controlled DMT1 as an adjunct to insulin in patients with a BMI ≥ 27 kg/m² when insulin alone does not provide adequate glycemic control despite optimal insulin therapy.

Epidemiological data

In Bulgaria, the prevalence of diabetes is about 7.9% of the population aged between 20 and 79 years. Of all patients with diabetes, the prevalence of DMT1 is about 10%.

Efficacy data

Two phase III clinical trials, DEPICT-1 and DEPICT-2, were conducted with dapagliflozin as an adjunct to adjustable insulin dose. These are 24-week randomized, double-blind, placebo-controlled clinical trials with a 28-week follow-up to evaluate efficacy and safety in adult patients with DMT1 and insufficient glycemic control (defined as HbA1c ≥ 7.5%) with insulin alone.

Decrease in glycated hemoglobin

In the summarized analysis of DEPICT-1 and DEPICT-2 studies, as well as in the subpopulation of patients with a BMI ≥ 27 kg/m², the proportion of those achieving a ≥ 0.5% reduction in HbA1c was significantly higher in the dapagliflozin group compared to placebo. Thus, 40-50% of patients treated with dapagliflozin achieved a reduction in HbA1c of 0.5% or more compared to 20-25% in the placebo arm. In the subgroup of patients with BMI ≥27 kg/m², the ratio was 47.2% versus 21.3%. This result persists through 52th week.

After 24 weeks of treatment, twice as many patients treated with dapagliflozin showed improved glycemic control without severe hypoglycaemia. Compared to placebo, the addition of dapagliflozin to insulin therapy in patients with DMT1 resulted in improved glycemic control without increasing the risk of hypoglycaemia.

Decreased glucose variability.

Changes in the mean amplitude of glucose excursion (MAGE) within 24 hours, reported with glucose monitoring systems (CGM) are significantly lesser in the group of dapagliflozin 5mg/10 mg versus placebo. In patients with a BMI ≥ 27 kg/m², glucose amplitude (a measure of glucose variability) decreased in the dapagliflozin 5 mg group compared to placebo.

Data confirm that the combination dapagliflozin + insulin significantly improves glycemic control and glucose variation in patients with DMT1.

Body weight
Dapagliflozin significantly reduced body weight in participants in DEPICT-1 and DEPICT-2, with results reported at 24th week. This is also the case in the subgroup of patients with BMI ≥ 27 kg/m². The tendency to lose weight continues after 24th week.

Reduction of the total insulin dose
The results of the studies show a significant reduction in the total dose of insulin received by patients. Dose reduction was observed during the first 2 weeks and was maintained for the duration of the study, including the follow-up phase. These results are statistically significant even after adjusting to patients' reduced body weight at week 24.

Reduction of blood pressure
A reduction in systolic blood pressure (SBP) in the sitting position was observed in dapagliflozin-treated patients, but the differences from baseline were not statistically significant.

Data reported by patients
The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and EQ-5D-3L were used to assess the impact of treatment on patient outcomes. The data show that dapagliflozin treatment improves patient satisfaction and preserves health-related quality of life (HRQoL).

Safety data

The safety profile of dapagliflozin in individuals with DMT1 is similar to the known safety profile of dapagliflozin in individuals with DMT2 except for the greater number of events with diabetic ketoacidosis in individuals with DMT1 treated with dapagliflozin. The most frequently reported adverse reactions with dapagliflozin in patients with DMT1 are genital infections, more frequent in women.

Data on comparators

Dapagliflozin is the only member of the SGLT-2 inhibitor group to be indicated as an adjunct to insulin therapy in patients with DMT1.
According to the Pharmacotherapeutic Guide to Endocrinology and Metabolic Diseases, intensive insulin therapy with fast-acting insulin/analogue before each meal and NPH insulin/basal insulin analogue is recommended. During remission, only an intermediate insulin/basal analogue, a fast-acting insulin/analogue or a conventional/analogue mixture may be administered.

Pharmacoeconomic indicators

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

A positive assessment of Forxiga health technology, performed by NICE, UK, has been published.

Applied analysis

Cost-effectiveness and cost-benefit pharmacoeconomic analyses were applied to evaluate the value efficacy of dapagliflozin for the treatment of insufficiently controlled DMT1 as an adjunct to insulin in patients with a BMI ≥ 27 kg/m², when insulin alone did not provide sufficient glycemic control despite optimal insulin therapy. Outcome measures are quality - adjusted life years (QALY) and years of life gained (LYG), as well as change in the values of glycated hemoglobin (HbA1c). The perspective is of the paying institution NHIF and only direct medication costs and ADR treatment costs are presented. The time horizon in the cost-benefit analysis is lifelong - 80 years. The time horizon for cost-effectiveness analysis is 1 year given the duration of the clinical trials - 52 weeks. Discounting with an annual discount factor of 3.5% is applied. A model is applied that allows to simulate the progression of the disease in an individual patient over a series of discrete time periods for the time horizon (80 years). As a comparator, insulin only therapy (bolus and basal) was selected, reflecting the clinical practice in Bulgaria.

<u>For the cost-effectiveness analysis</u>

Dapagliflozin therapy was cost-effective, with ICER values for 1 additional percent reduction in HbA1c and for 1 additional patient achieving a reduction in HbA1c of ≥ 0.5%, in both cases below the break-even point (between 1 and 3 times gross domestic product per capita).

<u>For the cost-benefit analysis</u>

Dapagliflozin therapy is cost-effective, with the additional cost of an additional QALY below the break-even point (between 1 and 3 times the gross domestic product per capita).
The applied sensitivity analysis confirms the conclusions made.
Subgroup analysis is not applied.

Costs for the assessed health technology

The cost of drug therapy with Forxiga and alternatives and the cost of treating complications have been calculated.

Budget impact analysis

The budget impact analysis was conducted from the point of view of the paying public institution. The time horizon is 5 years. The number of patients who will be treated with the

new therapy is expected to be 234 in the first year, reaching 2,806 in the fifth year. Forxiga, when covered by public funds, would lead to additional expenditure in the first year, which will increase each subsequent year over the five-year period, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Forxiga as an adjunct to insulin in adult patients with inadequately controlled DMT1 despite optimal insulin therapy and a BMI ≥ 27 kg/m² has a beneficial effect on overall glycemic control, glucose variability, body weight and insulin dosage.

The results of the pharmacoeconomic analysis show that Forxiga is a cost-effective alternative with ICER values below the break-even point. The use of the medicinal product Forxiga is expected to generate additional costs for the paying institution, which will increase every following year over the 5-year time horizon of the budget impact analysis, given the expected increase in the number of patients.