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

HEALTH TECHNOLOGY ASSESSMENT

Qtern

5 mg/10 mg film-coated tablet x 30

INN saxagliptin/dapagliflozin

Therapeutic indication(s)	Indicated in adults aged 18 years and older with type 2 diabetes mellitus: - to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Qtern do not provide adequate glycaemic control, - when already being treated with the free combination of dapagliflozin and saxagliptin.
Start/end date of procedure	13.05.2020 – 18.12.2020
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).and Annex 2 of the Positive Drug List (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 Qtern

Health problem

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood sugar levels, caused by impaired insulin secretion, insulin action, or both.

Diabetes mellitus is a chronic disease characterized by both acute and progressive development of macro- and microvascular complications. It is the chronic complications that determine the disability, 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 of the time of the diagnosis of type 2 diabetes or even in the pre-diabetic stage (micro- and macrovascular) and in the presence of insulin resistance (macrovascular).

The target population eligible for Qtern treatment is adult patients 18 years of age and older with DMT2 in whom metformin and/or sulphonylureas (SU) and one of the Qtern monocomponents do not provide sufficient glycemic control as well as patients already on treatment with the free combination of dapagliflozin and saxagliptin. Combining the effects of dapagliflozin (SGLT2 inhibitor) and saxagliptin (DPP-4 inhibitor) in one tablet allows patients to benefit from both pharmacological classes and at the same time reduces the need to take several tablets, the so-called pill burden. Reducing pill burden is a major factor in improving adherence to therapy and, accordingly, for improved glycemic control.

Epidemiological data
Data from the International Diabetes Federation from 2019 show that 8.3% of the population aged 20 to 79 has diabetes. For Bulgaria, the data indicate that half a million people suffer from diabetes. Mortality associated with diabetes in Bulgaria for 2019 is 6287 cases in the age group 20-79.

Efficacy data

The safety and efficacy of the fixed dose combination 5 mg saxagliptin/10 mg dapagliflozin was evaluated in three randomized, double-blind, active-controlled, placebo-controlled phase 3 clinical trials in 1,169 adult patients with diabetes mellitus - a clinical trial with saxagliptin and dapagliflozin added concomitantly to metformin, conducted for 24 weeks and two clinical adjunctive therapy studies in which dapagliflozin is added to saxagliptin plus metformin, or saxagliptin to dapagliflozin plus metformin, also conducted for 24 weeks, followed by a 28-week treatment extension period. The safety profile of the combined use of saxagliptin plus

dapagliflozin in these clinical trials up to 52 weeks is comparable to the profiles of safety of the monocomponents.

MB102129 is a phase 3 study to evaluate the safety and efficacy of dapagliflozin added to saxagliptin with metformin compared to placebo, added to saxagliptin with metformin in patients with DMT2 who have insufficient glycemic control with metformin and saxagliptin.

Study CV181168 is a phase 3 safety assessment study efficacy of treatment with saxagliptin added to dapagliflozin with metformin compared to placebo added to dapagliflozin with metformin in DMT2 subjects with insufficient glycemic control with metformin and dapagliflozin.

Study CV181169 is a multicenter randomized, double-blind, placebo-controlled, parallel phase III study of the safety and efficacy of adding saxagliptin and dapagliflozin to metformin compared with saxagliptin in combination with metformin or dapagliflozin in combination with metformin in patients with poorly controlled DMT2.

The primary endpoint for efficacy has been achieved; the treatment group with dapagliflozin + saxagliptin + metformin showed a statistically significant reduction compared to baseline glycated hemoglobin (HbA1c) versus the addition of placebo to saxagliptin + metformin (Study MB102129) and the addition of placebo to dapagliflozin + metformin (Study CV181168) over a 24-week period.

The results of the long - term extension (for studies MB102129 and CV181168) show that the reduction in HbA1c was permanent until the end of the 52-week period of treatment (the difference in mean change from baseline in HbA1c between the two therapeutic groups was - 0, 81% and - 0.20 for studies MB102129 and CV181168, respectively).

In both studies, the proportion of individuals who achieved therapeutic glycemic control response (defined as HbA1c < 7%) at week 24 was between 1.5 - 3 times higher in dapagliflozin or saxagliptin supplementation groups compared with placebo.

In study MB102129, the proportion of subjects reaching HbA1c < 7.0% at week 24 is more than 3 times higher in the dapagliflozin + saxagliptin + metformin group (38%) compared to the placebo + saxagliptin + metformin group (12.4%) and the difference was statistically significant. In study CV181168, the proportion of subjects reaching HbA1c < 7.0% at week 24 was over 1.5 times higher in the dapagliflozin + saxagliptin + metformin group (35.3%) than in the placebo group + dapagliflozin + metformin (23.1%).

The results of the long - term extension (for studies MB102129 and CV181168) show that the increase in the proportion of individuals who have achieved therapeutic glycemic response (defined as HbA1c < 7%) continued until the end of the 52-week treatment period (adjusted percent difference between the two treatment groups at week 52 was 16.8% and 16.2% for studies MB102129 and CV181168, respectively.)

Adjusted mean change at 24 weeks from baseline for postprandial glucose (PPG) at 2 hours showed no statistically significant effect of saxagliptin + dapagliflozin + metformin versus placebo + dapagliflozin + metformin in study CV181168.

Postprandial glucose (PPG) and fasting plasma glucose reductions (PGG) for the dapagliflozin + saxagliptin + metformin group are clinically significant and numerically greater than that achieved by adding saxagliptin to dapagliflozin + metformin on the 24th week for Study CV181168. Reductions in PPG and FGL for the dapagliflozin + group saxagliptin + metformin compared to the saxagliptin group were statistically significant in study MB102129.

The results of the long - term extension (for studies MB102129 and CV181168) show that the reduction of FGL from baseline is maintained until the end of the 52-week treatment period (the difference in the adjusted mean change from baseline at week 52 was 2.1 mmol/l and 0.4 mg/dL for studies MB102129 and CV181168 respectively).

In both studies, the treatment groups containing dapagliflozin had a score of -0.51 kg to - 2.39 kg decrease in mean corrected body weight relative to baseline at 24 weeks, even when treated with dapagliflozin during the open-air period treatment prior to randomization. The difference between treatment groups (dapagliflozin + saxagliptin + metformin versus placebo + saxagliptin + metformin) is statistically significant in study MB102129 but not in study CV181168.

In study CV181169, the saxagliptin and dapagliflozin group achieved significantly greater decrease in HbA1c, both relative to the saxagliptin group and relative to the dapagliflozin group after 24 weeks. Most patients have baseline HbA1c > 8%. The combination of saxagliptin and dapagliflozin added to metformin sequentially shows a greater decrease in HbA1c, regardless of baseline HbA1c, compared to saxagliptin or dapagliflozin added separately to metformin. In a subgroup analysis, the mean reduction from baseline HbA1c was usually greater in patients with higher baseline HbA1c.

Safety data

The combination of saxagliptin 5 mg and dapagliflozin 10 mg in adults with diabetes type 2 (DMT2) and insufficient glycemic control with metformin were evaluated in three

randomized, double-blind, active-controlled/placebo-controlled multicenter phase 3 clinical trials with parallel groups for up to 52 weeks. The safety profile of the combined use of saxagliptin plus dapagliflozin plus metformin is comparable to the adverse reactions found in the respective monocomponents.

Data on comparators

The following therapeutic alternatives are available in Bulgaria: free combination dapagliflozin and saxagliptin (+/- metformin), dapagliflozin (+/- metformin) and saxagliptin (+/- metformin). The fixed combination empagliflozin + linagliptin should also be considered as an available therapeutic alternative.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions for the purposes of another national healthcare system

An assessment of the health technology was carried out by TLV (Sweden) and a decision was made for reimbursement in line with the indication, approved by EMA.

Applied analysis

For comparative evaluation of the health technology, a cost-effectiveness economic analysis was chosen, in which the main outcome measure is change in the level of HbA1C (%) and the share of patients who reach target values of HbA1C (%), and cost-minimization, at which the measure of the outcome is the cost of treatment with the fixed and free dapagliflozin/saxagliptin combination. The perspective of analysis is that of the paying institution - the National Health Insurance Fund (NHIF). The time horizon is 1 year. Discounting and modeling are not applied. saxagliptin/metformin, dapagliflozin/metformin and dapagliflozin + saxagliptin are chosen as comparators. The fixed dose combination of dapagliflozin/metformin is associated with lower cost for the payer compared to the free combination. A deterministic sensitivity analysis was conducted.

Subgroup analyzes

Subgroups are not subject to the analysis.

Cost of the assessed health technology

The cost of drug therapy paid by the payer is included in the analysis.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the payer, the NHIF. The time horizon is 5 years. The expected number of patients for the first year is 1 270, and for the fifth it is 2 234. The analysis of the budget impact shows reduction of NHIF

expenditure over a five-year period, not taken into account risk-sharing agreements and patient access schemes.

Conclusion

Diabetes mellitus is a chronic disease characterized by macro- and microvascular complications of acute and progressive development. Qtern represents a fixed combination of saxagliptin + dapagliflozin, witht different mechanisms of action, at the same time reducing the need to take several tablets. The fixed combination improves adherence to therapy and accordingly improves glycemic control. The reimbursement of the assessed health technology will lead to cost savings for the NHIF for a five-year period.