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HEALTH TECHNOLOGY ASSESSMENT

Forxiga

10 mg film-coated tablet x 30 x 1 tablets (unit dose) blister

INN Dapagliflozin

Therapeutic indication(s)	For the treatment of symptomatic chronic heart failure in adults.
Start/end date of procedure	16.05.2023 – 10.11.2023
Final decision	Addition of a new therapeutic indication to Annex 1 of the Positive Drug List (PDL) for home treatment of diseases reimbursed 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 Forxiga

Health problem

Heart failure (HF) is not a standalone pathological diagnosis but a clinical syndrome characterized by fundamental symptoms such as dyspnea, lower extremity edema, and fatigue, which may be accompanied by physical signs including elevated jugular venous pressure, manifesting as distended neck veins and/or pulsations, pulmonary rales, peripheral edema, and others. The manifestations of HF result from structural and/or functional abnormal changes in the heart, leading to elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exertion. Most commonly, HF is associated with myocardial dysfunction—systolic, diastolic, or mixed. Pathological processes affecting the valvular apparatus, pericardium, and/or endocardium, as well as arrhythmias and conduction abnormalities, can also contribute to the development of HF.

Heart failure (HF) is categorized into several phenotypes based on left ventricular ejection fraction (LVEF) measurements. Heart failure with reduced ejection fraction (HFrEF) is defined as cases where LVEF is below 40%. Patients with LVEF between 41% and 49% are included in the group with mildly reduced LVEF or HFmrEF. Patients with LVEF above 50% are classified as having HF with preserved LVEF (HFpEF). Common risk factors include advanced age, comorbidities—particularly hypertension, chronic kidney disease, and type 2 diabetes mellitus, physical inactivity, weakness, and environmental stressors.

HFpEF is a multisystem disease that develops as a result of the complex interaction of multiple underlying pathophysiological abnormalities, which lead to reserve dysfunction or inability to adequately handle stress in multiple organs, ultimately resulting in clinical symptoms. In addition to the heart, reserve dysfunction involves the lungs, aorta, microvascular system, kidneys, gastrointestinal tract, adipose tissue, liver, and skeletal musculature.

Forxiga (dapagliflozin) is a selective and reversible inhibitor of SGLT2. It belongs to the class of medications used in diabetes management known as sodium-glucose co-transporter 2 (SGLT2) inhibitors, which are currently the most effective drug therapy available.

Epidemiological data

Globally, the number of patients with HF is around 64 million. The prevalence of HF in developed countries, and specifically age-related HF prevalence, has shown a decreasing trend in recent years. Currently, the incidence of diagnosed HF cases is approximately 3 per 1,000 patient-years (data for all age groups) or about 5 per 1,000 patient-years in adults. The prevalence of HF in adults is about 12%. The prevalence of HF increases with age: from approximately 1% in



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individuals under 70 years of age to about 10% in those over 70 years. Recently published studies on the prevalence of HF with preserved ejection fraction (HFpEF) in European Union populations show significant variability, ranging from 0.7 to 6.1 per 1,000 patient-years.

Efficacy data

The therapeutic efficacy and safety profile of dapagliflozin have been analyzed in one clinical trial.

The DELIVER trial is an international, multicenter, randomized, double-blind, placebo-controlled trial conducted in patients aged ≥ 40 years with heart failure (NYHA class II-IV) and left ventricular ejection fraction (LVEF) $> 40\%$, aimed at determining the effect of dapagliflozin compared to placebo on reducing the composite risk of cardiovascular death or worsening heart failure. In patients with heart failure and LVEF $> 40\%$, dapagliflozin demonstrated a statistically significant 18% reduction in the composite endpoint of cardiovascular death or worsening heart failure. Meta-analysis results show that the risk of cardiovascular death and hospitalizations for heart failure decreases progressively with increasing LVEF from below 25% to above 65%. Dapagliflozin reduces the risk of cardiovascular death or hospitalization for heart failure primarily through a 30% reduction in hospitalizations for heart failure across all patient groups regardless of their LVEF, with the effect attenuating when LVEF exceeds 65%. Patients treated with dapagliflozin have a lower rate of cardiovascular mortality or hospitalizations for heart failure compared to those receiving placebo. The effect of dapagliflozin on the risk of hospitalizations for heart failure and cardiovascular death is consistent across all pre-specified subgroups, including those with type 2 diabetes. The results from key clinical studies with dapagliflozin indicate that treatment with this medication is associated with improved quality of life as early as 8 weeks compared to placebo in patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF). Dapagliflozin positively affects kidney function by statistically significantly reducing the rate of deterioration in glomerular filtration rate throughout the follow-up period. Additionally, dapagliflozin has a favorable impact on diabetes parameters, reducing glycated hemoglobin levels compared to placebo. There were fewer cardiovascular deaths in the dapagliflozin group compared to the placebo group (231 vs. 261), but this difference was not statistically significant. There was also no significant difference in all-cause mortality between the dapagliflozin and placebo groups, with 497 (15.9%) and 526 (16.8%) deaths from any cause in the dapagliflozin and placebo groups, respectively (HR: 0.94; 95% CI: 0.83, 1.07).

Safety data

Dapagliflozin (Forxiga) is well-tolerated and no new safety concerns have been identified in patients with HF and left ventricular ejection fraction (LVEF) $> 40\%$. During and outside the treatment period, there were 507 deaths in the dapagliflozin group and 529 deaths in the placebo group. During treatment, the proportion of patients experiencing serious adverse events is balanced between groups: 43.5% in the dapagliflozin group and 45.5% in the placebo group. The three most



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commonly reported serious adverse events during treatment are heart failure, COVID-19, and pneumonia in both treatment arms.

Data on comparators

The comparative alternative in the model is the standard therapy for HFpEF. According to international and national standards, it includes the following classes of products and their respective representatives, reimbursed in Bulgaria:

- ACE Inhibitors: captopril, enalapril, lisinopril, ramipril, trandolapril;
- Beta-Blockers: bisoprolol, carvedilol, metoprolol, nebivolol;
- ARBs (Angiotensin Receptor Blockers): candesartan, valsartan, losartan;
- MRAs (Mineralocorticoid Receptor Antagonists): eplerenone.

As of April 2023, the Positive Drug List does not include specific treatments for HFpEF. The above-mentioned products are used either as monotherapy or in combination, depending on patient needs. SGLT2 inhibitors are the newest class of pharmacological products for the treatment of heart failure. Representatives include empagliflozin (Jardiance) and dapagliflozin (Forxiga), which currently provide the greatest clinical benefit.

Pharmacoeconomic indicators

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

A positive health technology assessment evaluating the use of dapagliflozin in patients with heart failure with preserved ejection fraction has been published by NICE, United Kingdom.

Applied analysis

A pharmacoeconomic analysis has been attached, which is a cost-effectiveness analysis (CEA), where the final outcome regarding health benefits is presented as life-years gained (LYG), and a cost-utility analysis (CUA), where the final outcome regarding health benefits is presented as quality-adjusted life-years (QALY). The analysis is conducted from the perspective of the payer institution – the National Health Insurance Fund. The time horizon of the analysis is lifetime. This time horizon reflects the chronic and progressive nature of heart failure and is consistent with the approach adopted in evaluating therapy for the examined population. All costs and outcomes in the model are discounted at an annual rate of 3.5%. The model reflects disease progression through transitions between discrete health states, defined by quartiles of the total symptom score (TSS) on the Kansas City Cardiomyopathy Questionnaire (KCCQ) (calculated for all patients at baseline, regardless of the type of treatment). KCCQ-TSS determines the frequency and severity of patients' symptoms. In addition to health states, the model accounts for the frequency of hospitalizations for heart failure (HHF) and urgent heart failure visits (UHFV). The results show that the probability of dapagliflozin + standard therapy being a cost-effective alternative compared to standard therapy



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alone is 93.7% at a cost-effectiveness threshold of 60,630 BGN (3 times the GDP per capita of Bulgaria). Additionally, treatment with dapagliflozin is associated with a reduction in hospitalization costs for patients with heart failure over the time horizon of the analysis.

Costs for the assessed health technology

The costs included in the model are costs for medication therapy for the evaluated health technology, costs for standard care treatment, and costs for managing adverse events.

Subgroup Analysis

No subgroup analyses have been conducted.

Budget impact analysis

The budget impact analysis has been conducted from the perspective of the payer institution – NHIF. The time horizon is 5 years. The budget impact analysis is presented in two scenarios. Scenario 1 evaluates the budget impact of dapagliflozin compared to the standard therapy reimbursed by NHIF as of July 2023. Scenario 2 examines the budget impact of reimbursing dapagliflozin under the assumption that empagliflozin is also reimbursed for the treatment of patients with HFpEF.

In Scenario 1, the analysis forecasts an increase in costs over a period of five years for the NHIF, considering the gradual inclusion of patients receiving dapagliflozin therapy. When accounting for savings resulting from reduced hospitalizations among patients treated with dapagliflozin, the budget impact of reimbursing Forxiga decreases by the fifth year, assuming no risk-sharing agreements or patient access schemes are considered.

The results from Scenario 2 indicate that the expected budget impact is negative due to the lower costs of treating with dapagliflozin compared to empagliflozin. It is assumed that the reimbursement of dapagliflozin will lead to savings for the payer institution, NHIF, over the time horizon of the analysis, without considering risk-sharing agreements and patient access schemes.

Conclusion

The health technology dapagliflozin (forxiga) belongs to the group of sodium-glucose co-transporter 2 (SGLT2) inhibitors. SGLT2 inhibitors are the latest class of pharmacological treatments for heart failure (HF). The results from the primary clinical trials with dapagliflozin (Forxiga) indicate that treatment with this drug is associated with a greater improvement in quality of life compared to placebo in patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with mid-range ejection fraction (HFmrEF). The results of the pharmacoeconomic analysis show that dapagliflozin plus standard therapy is a cost-effective alternative compared to standard therapy alone. Additionally, treatment with dapagliflozin is associated with reduced hospitalization costs for patients with heart failure over the time horizon of the analysis. The budget impact analysis indicates that in Scenario 1, an increase in costs is projected over a five-year period



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for NHIF, considering the gradual inclusion of patients on dapagliflozin therapy. The results from Scenario 2 show that Forxiga will lead to savings for NHIF due to the lower costs of pharmacotherapy with the assessed health technology, without considering risk-sharing agreements and patient access schemes.