



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



HEALTH TECHNOLOGY ASSESSMENT

Jardiance

10 mg film-coated tablet x 30

INN Empagliflozin

Therapeutic indication(s)	For treatment of adults with Chronic Kidney Disease (CKD)
Start/end date of procedure	28.07.2023 – 13.12.2023
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) and to Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act.



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

Health problem

Chronic kidney disease (CKD) is a progressive disorder characterized by a decline in kidney function and/or kidney damage. The clinical characteristics of CKD are similar regardless of the underlying etiology and include increased intraglomerular pressure, hyperfiltration, and albuminuria. These common characteristics result from shared pathological processes in the kidneys, including progressive loss of nephrons and reduced kidney function. CKD often progresses asymptotically in the early stages and is usually detected incidentally during urine and/or blood tests related to routine monitoring of other diseases or during routine screening. However, in the advanced stages of the disease, patients may report symptoms such as fatigue, poor appetite, nausea, vomiting, itching, changes in mental status, or peripheral edema. Reduced kidney function and kidney damage can lead to a range of complications in CKD patients, particularly progression to end-stage kidney disease (ESKD), anemia, dyslipidemia, heart failure, impaired bone metabolism, metabolic acidosis, hyperkalemia, infections, increased risk of fatal and non-fatal atherosclerotic cardiovascular events, and increased risk of all-cause mortality. The progression of CKD to more advanced stages and the increase in albuminuria are associated with the development of ESKD and an increased risk of adverse events, such as death and cardiovascular events, compared to earlier stages of the disease.

Currently, there are no approved treatments that can lead to the regression of kidney damage associated with CKD and restore kidney function. The treatment of patients diagnosed with CKD aims to slow or prevent disease progression and manage CKD-related complications. Therefore, timely diagnosis and early intervention are crucial in slowing the progression of CKD.

Empagliflozin (Jardiance) belongs to the class of medications used in diabetes treatment, known as sodium-glucose co-transporter 2 (SGLT2) inhibitors.

Efficacy data

The therapeutic efficacy and safety profile of empagliflozin were analyzed in one clinical trial:

The **EMPA-KIDNEY** clinical trial is a double-blind, multicenter, randomized, controlled, phase III clinical trial designed to investigate the effect of empagliflozin plus standard therapy (optimized dose of ACE inhibitor or ARB as the main renoprotective therapy) compared to placebo plus standard therapy on renal and cardiovascular events in a broad range of CKD patients, including those with type 2 diabetes (T2DM). Primary endpoints are the progression of kidney disease or cardiovascular death. Secondary endpoints include time to hospitalization for any cause, time to



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death from any cause, time to kidney disease progression, time to cardiovascular death, and time to cardiovascular death (CV death) or ESKD (end-stage kidney disease).

The results of the clinical trial showed that the primary outcome was a combination of kidney disease progression (defined as end-stage kidney disease, sustained reduction in the estimated glomerular filtration rate (eGFR) to <10 ml per minute per 1.73 m^2 , sustained reduction in eGFR by $\geq 40\%$ from baseline, or death from renal causes) or cardiovascular death. Hospitalizations for any cause were lower in the empagliflozin group than in the placebo group. All-cause mortality occurred in a smaller proportion of patients in the empagliflozin group compared to the placebo group, although the risk of all-cause mortality was not significantly reduced with empagliflozin treatment compared to placebo. Kidney disease progression (defined as end-stage kidney disease (ESKD), sustained reduction in eGFR to $<10\text{ mL/min/1.73m}^2$, renal death, or sustained reduction in eGFR by $\geq 40\%$ from baseline) was observed in a smaller proportion of patients in the empagliflozin group compared to the placebo group. The risk of kidney disease progression was significantly reduced with empagliflozin treatment compared to placebo. CV events occurred in a small proportion of patients in both treatment groups. CV death or ESKD occurred in a smaller proportion of participants in the empagliflozin group compared to the placebo group. Empagliflozin treatment significantly reduced the risk of CV death or ESKD compared to placebo. The trial was prematurely terminated due to the unequivocally positive effect and proven safety, with the results announced in early November 2022.

Safety data

The most common adverse drug reactions were metabolism and nutrition disorders, followed by infections, renal, and urinary disorders.

Data on comparators

A comparative alternative is the standard therapy with renin-angiotensin-aldosterone system inhibitors, which are first-line therapy in CKD patients and the already used dapagliflozin for this indication.

Pharmacoeconomic indicators

Attached analysis

A cost-effectiveness analysis (CEA) was conducted, where the health benefit outcome was presented as life years gained (LYG), and a cost-utility analysis (CUA), where the health benefit outcome was presented as quality-adjusted life years (QALY). Dapagliflozin was chosen as the comparative alternative. The analysis was conducted from the perspective of the payer – the National Health Insurance Fund (NHIF). The chosen time horizon is lifetime. Costs and outcomes



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are discounted at an annual discount rate of 3.5%. A microsimulation model was applied, tracking the evolution of CKD risk factors and their impact on disease outcomes.

The analysis results show that empagliflozin therapy leads to lower costs and better health outcomes compared to dapagliflozin, i.e., it is a dominant alternative.

Costs of the assessed health technology

The model included costs associated with treatment using the health technology and alternatives, as well as complication costs.

Subgroup analysis

None provided.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the payer – the NHIF. The time horizon is 5 years. The target population includes CKD patients as an addition to the standard therapy. The estimated number of patients in the first year is 1,100, and in the fifth year – 7,300. Two scenarios are considered: "World with Jardiance" and "World without Jardiance." The analysis forecasts an increase in costs over five years for the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The assessed health technology, empagliflozin (Jardiance), is an option to address unmet needs in CKD therapy, which could lead to regression of kidney damage associated with CKD, restore kidney function, and manage disease complications.

The pharmacoeconomic analysis results show that empagliflozin therapy leads to lower costs and better health outcomes compared to the main comparative alternative, dapagliflozin, making it a dominant alternative. Including Jardiance in the Positive Drug List for CKD treatment will result in additional costs for the payer.