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HEALTH TECHNOLOGY ASSESSMENT

Jardiance

10 mg film-coated tablet x 30

INN Empagliflozin

Therapeutic indication(s)	For the treatment of symptomatic chronic heart failure in adults.
Start/end date of procedure	01.07.2022 – 06.03.2023
Final decision	Rejects inclusion of a new therapeutic indication in 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 Jardiance

Health problem

Heart failure with preserved ejection fraction (HFpEF) is global pandemic, affecting half of the heart failure patients, with its incidence and prevalence expected to rise further with the aging population. Compared to heart failure with reduced ejection fraction (HFrEF), patients with HFpEF are more likely to be older, female and have a higher prevalence of cardiovascular high risk factors (e.g. obesity, hypertension, and diabetes), other cardiovascular comorbidities (e.g. atrial fibrillation and valvular disease) and non- cardiovascular comorbidities e.g., anemia, chronic lung disease and chronic kidney disease), but a lower prevalence of ischemic heart disease. A new category, heart failure with mid-range ejection fraction (HFmrEF), has been introduced for ejection fraction within the range of 40–49%, to emphasize that this range is not normal, but there are also no evidence-based interventions for it.

There is significant overlap in clinical characteristics, risk factors, types of cardiac remodeling, and outcomes among the ejection fraction categories of left ventricular ejection fraction (LVEF) in HF. Patients with HFmrEF generally have characteristics more similar to HFrEF than to HFpEF, being more likely to be male, younger, and have coronary artery disease (50-60%), and less likely to have atrial fibrillation (AF) and non-cardiac comorbidities. Indeed, ambulatory patients with HFmrEF have lower mortality than those with HFrEF, similar to those with HFpEF. Patients with HFmrEF may include those whose LVEF has improved from $\leq 40\%$ or has declined in cases with $\geq 50\%$. Only diuretics are class I recommendations for treatment and are recommended in patients with congestion and HFmrEF to alleviate symptoms and signs. HFpEF differs from HFrEF and HFmrEF in that patients with HFpEF are older and more often women. There are multiple potential causes for HFpEF. The pathophysiology of the different HFpEF syndromes differs and, therefore, they require different therapies. Diuretics are class I for treatment and are recommended in patients with edema and HFpEF to relieve symptoms and signs. Treating hypertension is recommended to prevent or delay the onset of HF and prevent HF hospitalizations. Treatment should be based on hypertension management recommendations. SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of cardiovascular disease or with cardiovascular disease to prevent HF hospitalizations. This recommendation is also class I.

Efficacy data

The therapeutic efficacy and safety profile of empagliflozin were analyzed in two clinical trials – EMPEROR-Preserved and EMPERIAL-Preserved, though the latter is not subject to analysis as it evaluates the effect on the 6-minute walk test. The EMPEROR-Preserved clinical trial is a



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randomized, double-blind, placebo-controlled, phase III trial, with a median follow-up duration of 26.2 months. Patients were randomized in a 1:1 ratio to receive oral empagliflozin 10 mg or matching placebo once daily. The primary endpoint was the time to first confirmed event of either cardiovascular (CV) death or hospitalization due to heart failure (hHF). Key secondary endpoints included the occurrence of confirmed hHF (first and recurrent) and the slope of the change in eGFR (CKD-EPI) from baseline, included in confirmatory testing as key secondary endpoints. The results from the EMPEROR-Preserved clinical trial show that the primary endpoint was met. Treatment with empagliflozin significantly reduced the total number of hHF compared to placebo. Compared to placebo, treatment with empagliflozin significantly slowed the rate of decline in eGFR.

Safety data

Adverse events leading to treatment discontinuation in the EMPEROR-Preserved trial occurred in 571 patients (19.1%) in the empagliflozin group and in 551 patients (18.4%) in the placebo group. Uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with empagliflozin.

Data on comparators

There is no specifically recommended treatment for chronic heart failure with preserved ejection fraction, and drugs with proven effectiveness aimed at the underlying diseases leading to heart failure are used.

Pharmacoeconomic indicators

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

Three assessments have been published by other government institutions - Haute Autorité de santé - HAS (France), Tandvårds- och läkemedelsförmånsverket – TLV (Sweden), Der Gemeinsame Bundesausschuss - G-BA (Germany). The HAS opinion is in favor of reimbursing Jardiance (empagliflozin) 10 mg for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) > 40%. According to TLV's analyses, the cost of treatment with Jardiance is reasonable for the entire field of use in heart failure. The G-BA opinion reports a small additional benefit.

Applied analysis



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A cost-effectiveness analysis (CEA) was conducted, where the final outcome in terms of health benefits is presented as life-years gained (LYG) and cost-utility analysis (CUA), where the final outcome in terms of health benefits is presented as quality-adjusted life-years (QALY) gained. As comparative alternatives, ACE inhibitors – captopril, enalapril, lisinopril, ramipril, trandolapril; Beta-blockers – bisoprolol, carvedilol, metoprolol, nebivolol; ARBs – candesartan, valsartan, losartan; ARNi – sacubitril/valsartan; MRAs – eplerenone were chosen. The analysis was conducted from the perspective of the paying institution – the National Health Insurance Fund (NHIF). The selected time horizon is lifetime. Costs and outcomes are discounted at an annual discount rate of 3.5%. A Markov model was applied, tracking patients according to disease severity and progression between different health states, determined by the Kansas City Cardiomyopathy Questionnaire clinical score – an instrument used to assess the quality of life in patients with heart failure. The results of the analysis show that ICER and ICUR fall below the threshold of 3 times the country's gross domestic product, i.e., the treatment of patients with heart failure with preserved or mid-range ejection fraction is a cost-effective therapy.

Costs for the assessed health technology

The model includes costs for treatment with Jardiance, costs for treatment with alternatives, costs for patient follow-up and hospitalization.

Subgroup analysis

No subgroup analysis was provided.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying institution – NHIF. The time horizon is 5 years. The target population includes patients with heart failure with preserved or mid-range ejection fraction (HFpEF/HFmrEF). The projected number of patients in the first year is 400, and in the fifth year – 5,156. Two scenarios are considered – "World with Jardiance" and "World without Jardiance." The analysis forecasts an increase in costs over a five-year period for the NHIF, with no consideration of risk-sharing agreements or patient access schemes.

Conclusion

Empagliflozin is a reversible, potent and selective competitive inhibitor of the sodium-glucose cotransporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters relevant to glucose transport in peripheral tissues and is 5000 times more selective for SGLT2 compared to SGLT1 (the main transporter responsible for glucose absorption in the intestines). The results of the conducted pharmacoeconomic analysis indicate that Jardiance, INN empagliflozin, has higher costs and more health benefits and is a cost-effective therapy.