



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



HEALTH ASSESMENT TECHNOLOGY

Jardiance

10 mg film-coated tablet x 30

INN Empagliflozin

Therapeutic indication(s)	For treatment of symptomatic chronic heart failure in adults.
Start/end date of procedure	23.03.2023 – 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), 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

Heart failure (HF) is clinically classified into HF with significantly reduced systolic function when the ejection fraction (EF) is below 40%; patients with a left ventricular EF between 41% and 49% are included in the group with mildly reduced left ventricular systolic function (HFmrEF), and patients with an EF above 50% are classified as having HF with preserved left ventricular systolic function (HFpEF). The prevalence of HF in adults is approximately 12%. HF prevalence increases with age: from about 1% in individuals under 70 years old to about 10% in individuals over 70 years old. The distribution of HF types is considered to be 50% of diagnosed patients with HFrEF and 50% with HFpEF or HFmrEF.

The clinical picture in HF patients has several main features: dyspnea at rest and with exertion, fatigue (reduced functional capacity), a tendency for a higher heart rate with/without a gallop rhythm, palpitations, and congestive physical signs (lung and/or peripheral edema). These symptoms and signs, however, lack good accuracy to be used alone for confirming HF diagnosis. HF diagnosis requires the presence of symptoms and/or signs of cardiac dysfunction. Depending on the underlying organic heart disease, additional symptoms related to its pathophysiology may manifest. HF diagnosis is more likely in patients with a history of myocardial infarction, arterial hypertension, coronary artery disease, diabetes mellitus, chronic kidney disease, cardiotoxic chemotherapy, or a history of sudden cardiac death.

Empagliflozin (Jardiance) is a molecule, orally active, potent, and selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2). It belongs to a new class of drugs initially developed as an antidiabetic agent. It mediates glucose reabsorption in the kidney. Approximately 90% of renal glucose reabsorption occurs in the first segment of the proximal tubule. The remaining 10% is removed in the distal segment through SGLT1 (a high-affinity, low-capacity transporter). SGLT2 inhibition reduces renal glucose reabsorption, induces more pronounced urinary excretion, and lowers plasma glucose concentrations. SGLT2 inhibition is also associated with weight loss caused by reduced caloric absorption through urinary excretion, as well as decreased subcutaneous and visceral fat tissue.

Epidemiological Data

Globally, there are about 64 million HF patients. The prevalence of HF in developed countries, particularly age-specific prevalence, has shown a trend towards reduction in recent years. This trend is linked to better treatment and earlier diagnosis, but overall prevalence in older age increases. The prevalence of diagnosed HF cases is about 3:1000 person-years (data for all age groups) or about 5:1000 person-years in adults.



Efficacy data

The **EMPEROR Preserved** clinical trial noted cardiovascular (CV) death in 219 patients on active treatment and 244 on placebo. HF hospitalizations were statistically lower in patients treated with empagliflozin (259 patients versus 352 on placebo). The primary endpoint (CV mortality or HF hospitalizations) was significantly lower in patients treated with empagliflozin. Over 26 months, the number needed to treat (NNT) to prevent one CV event was 31. Subgroup analysis confirmed that empagliflozin's effect on the primary endpoint was independent of baseline patient characteristics, including left ventricular ejection fraction levels, presence of diabetes, and blood pressure values. Clinical trials find that the benefit of empagliflozin in terms of morbidity is statistically significant.

Results from key clinical trials with empagliflozin show that treatment with the drug is associated with a greater improvement in quality of life compared to placebo in patients with HFpEF and HFmrEF. The improvement in quality of life indices is primarily due to the reduction in symptom frequency (adjusted mean difference - 2.3) and severity (2.01). A meta-analysis provides the latest data from known trials on major CV outcomes in patients treated with SGLT2 inhibitors to assess cardiorenal efficacy in patients with/without type 2 diabetes. Eleven large randomized clinical trials for CV outcomes were included in the analysis with 77,541 patients. The data are based on treatment with five SGLT2 inhibitors. Overall, the risk of composite CV mortality or HF hospitalizations decreases by 23% ($p < 0.001$) compared to placebo, without significant heterogeneity and without the influence of existing type 2 diabetes. The risk of CV mortality, overall mortality, and HF hospitalizations was reduced by 16%, 13%, and 32%, respectively. The risk of composite renal disease outcome decreased by 35%, with moderate heterogeneity.

In conclusion, from the main clinical trials in patients with HFpEF (including HFmrEF), empagliflozin (Jardiance) reduces the risk of cardiovascular death or HF hospitalizations in patients with preserved ejection fraction, including those with mildly reduced ejection fraction (reduction in the primary endpoint); results also show optimal NNT values for preventing one CV complication (equivalent to those obtained with statin treatment). The latest data confirm that empagliflozin (Jardiance) can provide benefits for all HF patients across the full spectrum of left ventricular ejection fraction values (from below 25% to 60%). Empagliflozin (Jardiance) has been proven to positively impact quality of life in HF patients as early as the 12th week of treatment initiation. Empagliflozin positively affects renal function by significantly slowing the rate of glomerular filtration decline throughout the follow-up period. Empagliflozin (Jardiance) induces clinically significant reduction in systolic blood pressure, improving disease outcomes, regardless of the likelihood of resistant hypertension. Empagliflozin (Jardiance) positively influences diabetes parameters: it reduces glycated hemoglobin levels compared to placebo, increases hematocrit in cases of anemia compared to placebo, and slightly reduces body weight and uric acid levels.



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Safety data

The most common adverse drug reactions are hypoglycemia (when used together with sulfonylureas or insulin) and hypovolemia.

Data on comparators

There is no specifically recommended treatment for chronic heart failure with preserved ejection fraction and drugs with proven efficacy targeting underlying conditions leading to heart failure are applied.

Pharmacoeconomic indicators

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

Two positive assessments have been published by other state institutions - HAS (France) and TLV (Sweden).

Applied analysis

The pharmacoeconomic analysis is a cost-effectiveness analysis (CEA), where health benefits are presented as life years gained (LYG) and a cost-utility analysis (CUA), where health benefits are presented as quality-adjusted life years (QALY). Comparative alternatives include ACE inhibitors (captopril, enalapril, lisinopril, ramipril, trandolapril); beta-blockers (bisoprolol, carvedilol, metoprolol, nebivolol); ARBs (candesartan, valsartan, losartan); ARNi (sacubitril/valsartan); MRAs (eplerenone). The analysis is conducted from the perspective of the paying institution - the National Health Insurance Fund (NHIF). The chosen time horizon is lifetime. Costs and outcomes are discounted at an annual rate of 3.5%. A Markov model, which tracks patients based on disease severity and progression between different health states defined by the Kansas City Cardiomyopathy Questionnaire clinical score - an instrument used to assess the quality of life in heart failure patients - is applied. The analysis results show that ICER and ICUR fall below the favorable threshold of 3 times the country's gross domestic product, making treatment of patients with heart failure with preserved or mildly reduced ejection fraction cost-effective.

Costs for the assessed health technology

The model includes costs for treatment with Jardiance and alternative treatments.

Subgroup analysis

Not applied.



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Budget impact analysis

The budget impact analysis is 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 mildly reduced ejection fraction (HFpEF/HFmrEF). The projected number of patients in the first year is 983, and in the fifth year - 6,191. Two scenarios are considered - "World with Jardiance" and "World without Jardiance." The analysis predicts an increase in costs over a five-year period for NHIF, without considering risk-sharing agreements and patient access schemes.

Conclusion

The health technology empagliflozin (Jardiance) achieves the main goals of pharmacotherapy in patients with HF, regardless of ejection fraction values (<25%, 41-49%, above 50%): reduction in mortality, prevention of hospitalizations, improvement in clinical status, and quality of life enhancement. Along with favorable effects on HF parameters, empagliflozin also exhibits additional effects: slowing the rate of glomerular filtration decline, lowering blood pressure values, improving endothelial function, and improving diabetes parameters. The budget impact analysis predicts an increase in NHIF expenses over a five-year period.