The cost-effectiveness of empagliflozin (Jardiance®) for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of empagliflozin for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction. Following NCPE assessment of the Applicant's submission, empagliflozin is considered cost-effective for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction and reimbursement is recommended*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Boehringer Ingelheim) Health Technology Assessment of empagliflozin. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **April 2022**

Summary

On the 12 January 2022 Boehringer Ingelheim submitted an economic dossier on the cost-effectiveness of empagliflozin (Jardiance®) for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction. Heart failure may be divided into different phenotypes based on left ventricular ejection fraction (LVEF) where a normal ejection fraction is ≥ 50%. Therefore, in heart failure with preserved ejection fraction (HFpEF) the recognised symptoms and signs are accompanied with a LVEF of ≥ 50%, with evidence of structural and/or functional cardiac abnormalities and/or elevated levels of natriuretic peptides. Heart failure with reduced ejection fraction (HFrEF) is accompanied with the recognised symptoms and signs and a LVEF ≤ 40%. Patients with a LVEF between 41% and 49% have mildly reduced left ventricular function designated as heart failure with mid-range ejection fraction (HFmrEF).

The current HSE-Medicines Management Programme (HSE-MMP) managed access protocol indicates that the standard of care for the treatment of chronic heart failure is an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) where ACE inhibitors are not tolerated. The angiotensin receptor-neprilysin inhibitor, sacubitril + valsartan (Entresto®) is only reimbursed for patients with HFrEF who remain symptomatic despite a stable dose of ACE or ARB. Patients with HFrEF should also be treated with beta blockers unless contraindicated. Loop diuretics such as furosemide or bumetanide will frequently be used. Mineralocorticoid inhibitors such as spironolactone may be added to therapy particularly in patients with an ejection fraction less than 35% and digoxin may be added for symptomatic control. Ivabradine may be used in chronic heart failure with systolic dysfunction, where the patient is in sinus rhythm and has a heart rate ≥ 70 beats per minute, in combination with standard therapy.

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2) and is indicated for the treatment of symptomatic chronic HFrEF. It is administered orally at a dose of 10 mg once daily and will be prescribed as an add-on to appropriate standard of care for adult patients with symptomatic chronic HFrEF.

1. Comparative effectiveness

The submitted dossier indicates that the EMPEROR-Reduced clinical trial provides the main evidence base for the clinical efficacy and safety of empagliflozin in the population with HFrEF. EMPEROR-Reduced was a double-blind trial where 3,730 patients (≥18 years) with New York Heart Association (NYHA) class II, III or IV heart failure and a left ventricular ejection fraction (LVEF) of 40% or less were randomised to receive empagliflozin 10mg once daily or placebo when added to recommended therapy. The mean age at baseline was approximately 67 years and 24% were female. In terms of NYHA classification 75%, 24% and 1% of participants has stage II, III and IV heart failure respectively. The mean LVEF was approximately 27% and the majority (> 70%) had a LVEF ≤ 30%. The median value for NT-proBNP was just over 1,800 pg/ml (< 125 pg/ml makes a diagnosis of HF unlikely) and the majority of participants (>78%) had an NT-proBNP exceeding 1,000 pg/ml. Just over 50% had ischaemic heart disease as the underlying cause of heart failure, 72% had a history of hypertension, over 35% had associated atrial fibrillation and 49.8% of participants had diabetes mellitus. All patients were receiving appropriate treatments for heart failure including, ACE inhibitors or ARBs (70.5%), sacubitril + valsartan (18.3%), beta-blockers (95%), mineralocorticoid receptor antagonists (70%) and diuretics.

The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure. During a median follow-up of 16 months, a primary outcome event occurred in 361 of 1,863 patients (19.4%) in the empagliflozin group and in 462 of 1,867 patients (24.7%) in the placebo group (hazard ratio (HR) 0.75;95% confidence interval(CI), 0.65 to 0.86; p<0.001). The impact of empagliflozin on the primary outcome was consistent regardless of the presence or absence of diabetes mellitus. The total number of hospitalizations for heart failure occurred in 388 (20.8%) patients in the empagliflozin group and in 553 (29.6%) in the placebo group (HR, 0.70; 95% CI, 0.58 to 0.85; p<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (-0.55 versus -2.28 ml/min/1.73m² of body surface area per year, p<0.001) and empagliflozin treated patients had a lower risk of serious renal outcomes. Death from any cause and cardiovascular mortality were 8% lower in the empagliflozin group but these differences did not reach statistical significance. The

median change in NT-proBNP from baseline to week 52 was -244 pg/ml in the empagliflozin group as compared with -141 pg/ml in the placebo group.

Patients' quality of life was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The change from baseline in health status was assessed at week 52 by the KCCQ clinical summary score (KCCQ-CSS) which measures heart failure symptom frequency, symptom burden and physical limitations. Empagliflozin significantly improved KCCQ-CSS by 1.94, 1.35 and 1.61 points compared to placebo at 3, 8 and 12 months ($p<0.05$ for all). A similar improvement was observed for the KCCQ total symptom score (KCCQ-TSS) and overall summary score (KCCQ-OSS) which includes a quality of life dimension. There were no relevant differences between the treatment groups in health-related quality of life using the EQ-5D questionnaire.

Sub-group analysis suggested that the magnitude of benefit was lower in the subgroup with NYHA class III – IV heart failure however a greater effect was seen in the subgroup with LVEF ≤ 30%. Of relevance to this submission, empagliflozin elicited favourable effects on cardiovascular death or hospitalization for heart failure regardless of receiving an angiotensin receptor-neprilysin inhibitor at baseline.

2. Safety

The median duration of follow-up in the EMPEROR-Reduced trial was 16 months and 61% of patients were treated for at least one year. The overall frequency of serious adverse events was lower in the empagliflozin group as compared with placebo, consistent with the efficacy analysis of all-cause hospitalizations. The most frequent serious adverse events included cardiac disorders (e.g. cardiac failure, ventricular tachycardia, atrial fibrillation), pneumonia and acute renal dysfunction. All other serious adverse events were reported in less than 3% of patients. Uncomplicated genital tract infections occurred more frequently in the empagliflozin group as did volume depletion and hypotension. There was no increase in hypoglycaemic events for patients with or without type II diabetes mellitus.

3. Cost effectiveness

The comparator included in this economic evaluation is current standard of care for heart failure with reduced ejection fraction. It is assumed that patients received appropriately titrated doses of agents such as ACE inhibitors, ARBs or angiotensin-receptor neprilysin inhibitor therapy. The cost-effectiveness model is a cohort-based Markov state-transition model developed in Microsoft Excel® to undertake a cost-utility analysis. The model describes the clinical course of HFrEF using five discrete health states, defined by quartiles of the baseline distribution of KCCQ-CSS in the combined treatment groups in EMPEROR-Reduced, with higher scores corresponding to a better health status. Death was the final health state. The model also captures empagliflozin's capacity to slow the progression of renal impairment. The patient cohort enters the model according to the baseline distribution of KCCQ-CSS quartiles. From this state, patients can transition to a higher (lower disease burden) or lower (higher disease burden) KCCQ-CSS quartile, remain in the same health state or die. In each of the health states patients can experience adverse events of hospitalization due to heart failure or a composite renal outcome. Transitions between health states (derived from EMPEROR-Reduced data) occur in one-month cycles with half-cycle correction was applied. The model captures the occurrence of first and subsequent hospitalization due to heart failure and treatment related adverse effects as transient events. Transition to the death state is modelled using parametric survival equations for cardiovascular mortality and all-cause mortality. Patients can discontinue empagliflozin at any cycle, thereafter they assume the same event rates and health state transition probabilities as patients receiving placebo. The utility and disutility values associated with the model health states, adverse events and hospitalisation for heart failure were obtained from the pooled analysis of the patient level data for the intention to treat population in EMPEROR-Reduced. Resource usage and costs considered in the model included direct medical costs for treatment acquisition, clinical event management and disease management costs. Results in the base case represent the perspective of the Health Service Executive (HSE). A discount rate of 4% was applied to costs and health outcomes.

A deterministic analysis of the cost-effectiveness of empagliflozin as add-on therapy to the standard of care was associated with incremental costs of €740 and an incremental quality adjusted life-year (QALY) of 0.19 resulting in a base case incremental cost-effectiveness ratio (ICER) of €3,879/QALY. Probabilistic analysis also resulted in a mean ICER of €3,879/QALY

and the probability of cost-effectiveness at the €45,000/QALY threshold was 88%. The deterministic sensitivity analysis highlighted the parameters that impacted the cost-effectiveness to the greatest extent including the treatment effect of empagliflozin plus standard of care on hospitalization for heart failure, discount rates for costs and health outcomes and the treatment effect of empagliflozin plus standard of care on all-cause mortality. The ICER for empagliflozin plus standard of care remained below €11,000/QALY across all parameter variations of interest.

4. Budget impact

The price to wholesaler of empagliflozin 10mg is €36.27 for a pack size of 28 tablets. The total cost per patient per annum is estimated at €556.42 (inclusive of mark-up, rebates and pharmacy fees). It was estimated that the number of patients treated with empagliflozin increased from 1,062 in year 1 to 8,443 in year 5 resulting in a 5-year gross budget impact of €12.1 million. The Applicant suggested that the 5 year net budget impact would result in savings, however the NCPE Review Group considered this highly unlikely.

5. Conclusion

The NCPE considers empagliflozin to be a cost-effective treatment for adults with symptomatic chronic heart failure with reduced ejection fraction and reimbursement is recommended*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.