SMC2523

empagliflozin film-coated tablet (Jardiance®)

Boehringer Ingelheim Ltd

07 April 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

empagliflozin (Jardiance®) is accepted for use within NHSScotland.

Indication under review: in adults for the treatment of symptomatic chronic heart failure with preserved ejection fraction (left ventricular ejection fraction [LVEF] >40%).

In a phase III study of adults with symptomatic chronic heart failure and LVEF >40%, the addition of empagliflozin to standard of care significantly improved time to first hospitalisation for heart failure or cardiovascular death.

SMC has issued separate advice for empagliflozin in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction (SMC2396).

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1 Medicine background

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor. It reduces reabsorption of sodium and increases delivery of sodium to the distal tubule, thereby increasing sodium excretion. This may lead to lowering of pre- and afterload of the heart, downregulating of sympathetic activity and reducing left ventricular wall stress as evidenced by lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) values and beneficial effects on cardiac remodelling, filling pressures and diastolic function.[1]

Empagliflozin is administered orally at a dose of 10mg once daily.[1]

1.2 Disease background

Chronic heart failure is a progressive condition, characterised by increasing inability of the heart to supply blood to meet tissue metabolic demands or the development of elevated left ventricular filling pressure to provide adequate blood supply. Symptoms include dyspnoea, oedema, cough, wheezing, tiredness, fatigue, reduced appetite, nausea, confusion and increased heart rate. Patients frequently require hospitalisation and have an increased risk of premature death. The New York Heart Association (NYHA) Functional Classification, categorises patients based on limitation of physical activity, ranging from class I, no limitation of physical activity, to class IV, unable to carry on any physical activity without discomfort. Patients can also be categorised based on left ventricular ejection fraction (LVEF), where reduced ejection fraction is defined as LVEF ≤40% and preserved ejection fraction is LVEF >40%, although some consider that LVEF >40% and <50% represents mid-range LVEF. Patients with preserved ejection fraction differ from patients with reduced ejection fraction; they tend to be older and more often female, with higher rates of atrial fibrillation, chronic kidney disease and non-cardiovascular co-morbidities.[2, 3]

1.3 Company proposed positioning

In July 2021, empagliflozin was licensed in the UK in adults for treatment of symptomatic chronic heart failure with reduced ejection fraction and SMC published advice (SMC2396) that accepted it for use in this indication. In June 2022, the licence was extended to include patients with symptomatic chronic heart failure with preserved ejection fraction and the indication was altered to remove the criterion: 'with reduced ejection fraction'. The current submission relates to the licence extension in patients with preserved ejection fraction, that is, LVEF >40%.

1.4 Treatment pathway and relevant comparators

Patients with preserved ejection fraction (LVEF >40%) are managed by treating co-morbidities and controlling congestive symptoms, usually with diuretics. Although there is no evidence of a disease modifying effect, patients are often treated with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers or mineralocorticoid receptor antagonists for underlying hypertension or coronary artery disease. There is an unmet need for therapies to reduce the risks of mortality and hospitalisation in patients with preserved ejection fraction.[2, 3]

In December 2022, the SGLT2 inhibitor, dapagliflozin, was also licensed for use in patients with chronic heart failure and preserved ejection fraction.[4] However, the timing of this new indication for dapagliflozin precludes it from being considered a relevant comparator in this submission.

2. Summary of Clinical Evidence

2.1 Evidence for the licensed indication under review

The clinical evidence for empagliflozin in chronic heart failure with preserved ejection fraction is from the EMPEROR-preserved study detailed in Table 2.1 below.[2]

Table 2.1. Overview of relevant study

Criteria	EMPEROR-preserved.[2]
Study Design	International, double-blind, phase III study.
Eligible Patients	Adults with NYHA class II-IV chronic heart failure, LVEF >40% and NT-proBNP level >300 pg/mL, or, for patients with atrial fibrillation NT-proBNP >900 pg/mL.
Treatments	Empagliflozin 10mg orally once daily or placebo until required number of primary outcomes events occurred. Concomitant usual heart failure therapies.
Randomisation	Randomisation was stratified by region, diabetes status, eGFR (<60 or ≥60 mL/minute/1.73m^2) and LVEF (<50% or ≥50%) and patients equally assigned.
Primary outcome	Time to first adjudicated cardiovascular death or hospitalisation for heart failure assessed in all randomised patients.
Secondary outcomes	Adjudicated hospitalisation for heart failure (first and recurrent events), then change from baseline in rate of decline in eGFR during double-blind treatment.
Statistical analysis	Key secondary outcomes tested in hierarchy if primary outcome significant.

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

At the final analysis (cut-off 26 April 2021), median follow-up was 26.2 months. Empagliflozin, compared with placebo, significantly improved the primary outcome, time to first hospitalisation for heart failure or cardiovascular death. The two key secondary endpoints in the hierarchical testing strategy were significantly improved with empagliflozin: (1) adjudicated hospitalisation for heart failure (first and recurrent); and (2) rate of decline in eGFR during double-blind treatment. Other secondary outcomes, such as mortality, were not formally tested. All-cause mortality was similar across the groups (14% in both). Analyses did not find any increase in a specific cause of non-cardiovascular death with empagliflozin. Results are detailed in Table 2.2 below.[2, 5]

Table 2.2: Outcomes of EMPEROR-preserved study.[2, 5]

	Empagliflozin (N=2,997)	Placebo (N=2,991)	Hazard ratio or difference (95% CI)[c]
First HF hospitalisation or CV death[a]	415 (14%)	511 (17%)	0.79 (0.69, 0.90)*
HF hospitalisation (as first event)	259 (8.6%)	352 (12%)	
CV death (as first event)	156 (5.2%)	159 (5.3%)	
All hospitalisations for HF, events[b]	407	541	0.73 (0.61, 0.88)*
Change in mean eGFR slope per year[b]	-1.25	-2.62	1.36 (1.06, 1.66)*
All-cause mortality[d]	422 (14%)	427 (14%)	1.00 (0.87, 1.15)
CV death[d]	219 (7.3%)	244 (8.2%)	0.91 (0.76, 1.09)
Non-CV death[d]	203 (6.8%)	183 (6.1%)	1.13 (0.92, 1.38)

* significant in the hierarchical testing strategy; a = primary outcome; b = key secondary outcomes; c = all hazard ratio, except change in mean eGFR slope per year; d = in any order (i.e. not first event)
CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate in mL/minute/1.73m^2; HF = heart failure.

2.2 Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using EuroQoL 5 dimensions (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ summary and domain scores range from 0 to 100. Change from baseline to week 52 in KCCQ clinical summary score was a secondary outcome that was not in the hierarchical testing strategy. For this outcome, placebo-corrected adjusted mean change from baseline was 1.32 (95% confidence interval [CI]: 0.45 to 2.19). The placebo-corrected adjusted mean change from baseline to week 52 for the seven domains were: 0.58 for physical limitation; -0.23 for symptom stability; 1.91 for symptom frequency; 1.89 for symptom burden; -0.24 for self-efficacy; 1.23 for quality of life; and 1.46 social limitation. There was a small difference in the proportion of patients achieving a clinically relevant change (5 points) in KCCQ clinical summary score with empagliflozin compared with placebo: 42% versus 39%. A regulatory review concluded that these treatment differences are small and not clinically relevant.[2] It was noted in the submission that there were no relevant differences between the treatment groups with regards to HRQoL as assessed by the EQ-5D questionnaire.

2.3 Supportive studies

A double-blind study (EMPERIAL-preserved) recruited 315 adults similar to those in the EMPEROR-preserved study (heart failure with LVEF >40% and NYHA class II to IV) who had a 6-minute walk test (6MWT) distance of ≥100m at baseline and ≤350m at screening and baseline. The primary endpoint, change in 6MWT distance from baseline to week 12, was not significantly different between empagliflozin and placebo. A regulatory review concluded that the study does not support an effect of empagliflozin on functional capacity and heart failure-related symptoms.[2 6]

A double-blind study (EMPA-VISION) recruited adults with chronic heart failure. In the 26 patients (Cohort B) who comprised the per protocol population with preserved ejection fraction (LVEF ≥50%), the primary outcome, change from baseline to week 12 in the ratio of phosphocreatine to adenosine triphosphate (PCr/ATP), was not significantly different with empagliflozin versus placebo: 0.100 versus 0.259, with an adjusted mean difference of -0.159 (95% CI: -0.604 to 0.286), p=0.4650. A regulatory review noted the following limitations: imbalances in baseline characteristics, a smaller than expected population; and fewer than estimated patients with diabetes.[2, 7]

3. Summary of Safety Evidence

A regulatory review concluded that studies with empagliflozin in patients with heart failure and preserved ejection fraction generally revealed no new major safety findings compared with the known safety profile of empagliflozin in patients with heart failure and reduced ejection fraction and/or type 2 diabetes mellitus.[2]

In the EMPEROR-preserved study, within the empagliflozin and placebo groups adverse events of interest included hypoglycaemia events (defined as plasma glucose ≤70mg/dL or that required assistance), 2.4% versus 2.6%, with rates of 4.3% versus 4.5% in patients with diabetes and 0.7% versus 0.8% in patients without diabetes. Hypotension was reported by 10% of patients in the empagliflozin group versus 8.6% of patients in the placebo group and was symptomatic in 6.6% versus 5.2%, respectively. Urinary tract infections occurred in 9.9% versus 8.1% of patients and

genital infections in 2.2% versus 0.7% of patients, with similar rates across the treatment groups for complicated urinary and genital infections.[5]

Similarly, in pooled data (EMPEROR-preserved, EMPEROR-reduced, EMPA-VISION, EMPERIAL-preserved and EMPERIAL-reduced), frequencies of acute renal failure, ketoacidosis, confirmed hypoglycaemic events, bone fractures and urinary tract malignancies were similar in the empagliflozin and placebo groups. Urinary tract infections, genital infections and volume depletion, including hypotension, were more common in the empagliflozin group than in the placebo group. Fewer patients in the empagliflozin group had hepatic injury events.[2]

4. Summary of Clinical Effectiveness Considerations

4.1 Key strengths

- Empagliflozin was the first SGLT2 inhibitor to be licensed for treatment of symptomatic chronic heart failure in patients with preserved ejection fraction (LVEF >40%).[2, 5]
- Empagliflozin compared with placebo significantly improved the time to first hospitalisation for heart failure or cardiovascular death, mainly due to reductions in hospitalisations for heart failure. Empagliflozin also significantly improved the rate of all (first and recurrent) hospitalisations for heart failure. These effects were considered clinically relevant in a regulatory review.[2, 5]

4.2 Key uncertainties

- The absolute difference in the primary outcome, 3.3%, appears to be due to an absolute difference in first hospitalisations of 3.2%.[2]
- All-cause mortality and cardiovascular mortality alone were not included in the hierarchical testing strategy of EMPEROR-preserved. The study was not powered to formally test these outcomes. Therefore, definitive conclusions cannot be reached. However, all-cause mortality appeared similar across the empagliflozin and placebo groups.[2]
- A regulatory review noted that assessment of the key secondary renal endpoint, change from baseline in eGFR slope, was limited by study duration, with a longer treatment period of more than 2 years needed to confirm a beneficial effect.[2]
- In the subgroup analysis of the primary outcomes by LVEF, the HRs (95% CI) were 0.71 (0.57 to 0.88), 0.80 (0.64 to 0.99) and 0.87 (0.69 to 1.1) in patients with LVEF <50%, 50% to <60%, and ≥60%, respectively. A regulatory review noted that, although the p-value for interaction was not significant (p=0.2098), the effect was more pronounced in patients with LVEF <50% compared with ≥60%. However, as empagliflozin had a beneficial effect in all LVEF subgroups, the indication for treatment of heart failure in patients with preserved ejection fraction was considered acceptable.[2]
- Almost all patients (94%) in EMPEROR-preserved had structural heart disease (that is, left atrial enlargement and/or left ventricular hypertrophy), with only 6% recruited solely on the basis of hospitalisation for heart failure within the preceding 12 months. The cause of heart failure was ischaemia in 35% of patients, hypertension in 36%, valvular heart disease in 5.9%, diabetes in 2.1%, alcoholism in 0.2%, idiopathic in 9.2% and other in 11%. The

study excluded patients with infiltrative diseases, such as amyloidosis, that are known to cause heart failure with preserved ejection fraction because diagnosis can be made quite late, they can have poor prognosis or (Takotsubo cardiomyopathy) could completely resolve. It was considered that patients known to have one of these conditions would have a substantially different risk of a primary outcome event than the rest of the study population. Therefore, the Summary of Product Characteristics (SPC) notes that efficacy has not been established in patients with infiltrative disease or with Takotsubo cardiomyopathy. Patients were also excluded if they had cardiomyopathy based on accumulation diseases (such as Fabry disease or haemochromatosis), muscular dystrophies, reversible causes (such as stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction. Also, the majority of patients had NYHA class II or III disease, with only 0.1% and 0.3% having class I and IV disease, respectively. The study does not provide evidence for the latter groups.[2]

4.3 Clinical expert input

Clinical experts consulted by SMC note that empagliflozin in the treatment of chronic heart failure with preserved ejection fraction is a therapeutic advance due to reductions in hospitalisations for heart failure. They consider that it would be added to optimised treatment for patients who remain symptomatic and may be particularly useful for those with mid-range chronic heart failure (LVEF between 40% and an upper cut-off of 50% to 60%).

4.4 Service implications

Clinical experts consulted by SMC note that the introduction of empagliflozin for chronic heart failure with preserved ejection fraction may impact the service through requirements for additional clinical services to manage these patients.

5. Summary of Patient and Carer Involvement

No patient group submission was received.

6. Summary of Comparative Health Economic Evidence

6.1 Economic case

The economic case is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime – 28 years based on an assumed mean starting age of 71.9 years
Population	Adult patients with symptomatic chronic heart failure with left ventricle ejection fraction (LVEF) >40%.
Comparators	Empagliflozin was considered as an add-on treatment to standard of care (SoC). SoC comprised of treatment with ACE inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, beta blockers and loop diuretics.

Model description	The model was a 5 state Markov model, featuring 4 health states based on the KCCQ clinical summary scores (CSS) and an absorbing death state. The KCCQ-CSS states were defined based on the quartile ranges of KCCQ-CSS reported by patients at the start of the central study EMPEROR-Preserved, with a higher KCCQ-CSS representing better health.[2, 5] Hospitalisation from heart failure (HHF) and adverse events were modelled using transient states.
Clinical data	The central source of clinical data was the EMPEROR-Preserved study. It informed the clinical data on transition probabilities, hospitalisation, adverse events and mortality.
Extrapolation	Transition probabilities between the KCCQ-CSS states were informed through the observed movements in the study, with transition probabilities stabilised after 9 months and assumed constant across the remainder of the model. The number of HHF events per cycle were based on a Poisson regression, which included the variables of KCCQ-CSS state and empagliflozin treatment status. That meant both factors determined the expected rate of hospitalisations. Time since treatment initiation was not included as an explanatory factor in the base case. The rates of adverse events were constant, and in line with those estimated from study data. For mortality, the company fitted Weibull curves to the time to event data from EMPEROR-Preserved. Two types of mortality were estimated, CV related mortality and all-cause mortality. Non-CV related mortality was defined as being equal to the difference between the two. Empagliflozin was assumed to have a treatment effect in reducing CV mortality, but not on all-cause mortality. Empagliflozin was subjected to a discontinuation rate, estimated from study data to which a generalised gamma function was applied. No discontinuation of SoC was included. Patients discontinuing empagliflozin were assumed to revert to the SoC transition probabilities and HHF, adverse event and mortality rates immediately.
Quality of life	HRQoL was estimated from EQ-5D-3L data collected in the EMPEROR-Preserved study. An additional adjustment was made as some of the resulting health state utility estimates were above those from the age-matched general population. An additional disutility was applied to account for HHF events.
Costs and resource use	Medicine costs covered the acquisition of empagliflozin, SoC and the treatment of adverse events. Wider costs covered monitoring of a patient's health, the treatment of HHF and a terminal care cost of those dying of CV related issues. No mortality cost was applied for those dying of non-CV causes.
Patient Access Scheme (PAS)	No PAS is in place for either empagliflozin or elements of SoC.

6.2 Results

The base case results estimated that empagliflozin would increase costs, mainly through medicine acquisition costs, which were only partially offset by lower HHF and cardiovascular death costs. At the same time empagliflozin was estimated at increasing quality of life through longer occupancy of the better KCCQ-CSS health states and reduced HHF. These results are summarised in the table below.

Table 6.2 Base case results

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£16,265	6.79	4.20	-	-	-	-
Empagliflozin + SoC	£17,937	6.86	4.29	£1,736	0.074	0.095	£17,582

SoC = standard of care, LYG = Life year gains, QALYs = quality adjusted life years, ICER = incremental quality adjusted life year

6.3 Sensitivity analyses

The company provided a variety of analyses to explore uncertainty within the model. The analysis showed that the economic results for empagliflozin are quite stable across a variety of input changes. SMC is unable to publish the scenario analysis results due to confidentiality issues.

*Other data were also assessed but remain confidential.**

Table 6.3 Selected scenario analysis

#	Input	Scenario description	Base case description
	Transition probabilities		
1	Long term probabilities	Long term transition probabilities based on observed study data from 4-8 months	Long term transition probabilities based on observed study data from 9+ months
2	Treatment waning	Transition probabilities equalise between empagliflozin and SoC arms at 5 years	No treatment waning. Transition probabilities remain constant from 9 months onwards
3		Transition probabilities equalize between empagliflozin and SoC arms at 10 years	
	Mortality		
4	Treatment effect of empagliflozin on mortality	Empagliflozin estimated as having a treatment effect on CV mortality and all-cause mortality	Empagliflozin estimated as having treatment effect on CV mortality only
5		Empagliflozin estimated as having no treatment effect on CV mortality or all-cause mortality	
6	Non-CV death costs	CV deaths and non-CV deaths both incur a cost of £4,295.	CV deaths incur a cost of £4,295. Non-CV deaths incur a cost of £0.
	Hospitalisation for health failure		
7	Time as a predictor of hospitalisation	Extended list of coefficients used in regression predicting HHF, including time effect	No time related coefficients used in regression predicting HHF
8	HHF treatment effect	Empagliflozin associated with no reduction in incidence of HHF	Empagliflozin assumed to reduce incidence of HHF
	Empagliflozin discontinuation		
9	Discontinuation	No discontinuation of empagliflozin	Empagliflozin discontinuation modelled on observed rate in the EMPEROR-Preserved study
	Utilities		
10	General population utility level correction	Utility values as initially derived from EMPEROR-Preserved study	Utility values across all health states down weighted based on UK general population values
	Time horizon		
11	Time horizon	35 year time horizon	28 year time horizon
12		20 year time horizon	
	Combined scenarios		
13	Assessment Team requested combined scenario	No adjustment to CV mortality, mortality costs equalized across CV and non-CV mortality & time-effect included in HHF regression	-

SoC = standard of care, ICER = incremental quality adjusted life year, CV = cardiovascular, HHF = hospitalisation due to heart failure

6.4 Key strengths

- The economic analysis aligned with the population covered in licence extension.
- The model structure was appropriate and matched that used in previous submissions to HTA bodies in a similar target population.
- The clinical data were taken from a large randomised and placebo controlled phase III study.

6.5 Key uncertainties

- Disaggregated economic results indicated a reduction in the number of HHF events was only a small contributor towards the differences in costs and health outcomes between the treatment arms. In particular, the difference in health outcomes was primarily driven by the length of occupancy of the better KCCQ states. This situation appears contradictory to the clinical evidence, which focused on the ability of empagliflozin to reduce the incidence of HHF.
- The method used by the company to estimate the disutilities of an HHF event across time was appropriate. However, the subsequent manipulation and application of those disutility values may have introduced a significant degree of error. The overall disutility was applied for 12 months, meaning that this quality adjusted life year loss would occur for each HHF event. This was felt to lack face validity and was not in keeping with values estimated from the literature.[8] Pragmatic exploration of the model by the SMC suggested using alternative approaches to the disutility would increase the incremental cost effectiveness ratio. While this increase was proportionally large, it was not sufficient to significantly alter the interpretation of the economic case.

7. Conclusion

After considering all the available evidence, the Committee accepted empagliflozin for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) publication number 147, 'Management of chronic heart failure' was published in March 2016. See here.[9]

The National Institute for Health and Care Excellence (NICE) guideline 106 (NG106), 'Chronic heart failure in adults: diagnosis and management' was published in September 2018. See here.[10]

The European Society of Cardiology (ESC) '2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure' were published in August 2021. See here.[3]

9. Additional Information

9.1 Product availability date

19 June 2022

9.2 Summary of product characteristics

See SPC for further information including dosing and safety. Empagliflozin 10mg and 25mg film-coated tablets (Jardiance®) SPC

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Empagliflozin	**10mg orally once daily**	**476**

Costs from BNF online on 14 December 2022. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 15,279 patients eligible for treatment with empagliflozin in year 1 rising to 15,556 patients in year 5, to which confidential uptake rates were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget impact.

*Other data were also assessed but remain confidential.**

References

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9. Scottish Intercollegiate Guidelines Network (SIGN). Publication 147: Management of chronic heart failure, March 2016. .
10. National Institute for Health and Care Excellence (NICE). NICE guideline 106 (NG106): Chronic heart failure in adults: diagnosis and management, September 2018. .

This assessment is based on data submitted by the applicant company up to and including 17 March 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the

individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.