Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2642

empagliflozin film-coated tablets (Jardiance®)

Boehringer Ingelheim

07 June 2024

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

ADVICE: following a full submission

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

Indication under review: in adults for the treatment of chronic kidney disease.

SMC restriction: in patients having individually optimised standard care (including angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, unless these are contraindicated or not tolerated), and either, at the start of treatment:

- an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73m^2 up to 45 mL/min/1.73m^2, or
- an eGFR of 45 mL/min/1.73m^2 up to 90 mL/min/1.73m^2 and either:
    - A urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more, or
    - Type 2 Diabetes Mellitus (T2DM).

In a randomised, double-blind, phase III study in patients with chronic kidney disease, treatment with empagliflozin added to standard of care significantly reduced the risk of first occurrence of progression of kidney disease or death from cardiovascular causes when compared with standard of care alone.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that reduces sodium reabsorption from the kidney resulting in activation of a tubuloglomerular feedback mechanism, renin-angiotensin-aldosterone system (RAAS) inhibition, decreased sympathetic nerve activity and increased hematocrit. Furthermore, metabolic effects on renal energy supply, local anti-inflammatory, anti-remodelling and anti-oxidative effects of empagliflozin may contribute to the beneficial effects of empagliflozin in patients with chronic kidney disease (CKD), although research is ongoing. The recommended dose of empagliflozin for CKD is 10 mg orally once daily.[1, 2]

1.2. Disease background

Chronic kidney disease is a progressive condition that results in the deterioration of kidney function and is a prominent global health issue that affects more than 10% of people worldwide. CKD can arise from a variety of difference causes, such as diabetes, hypertension, vascular disease, or glomerulonephritis. Uncontrolled diabetes and hypertension are the most common causes. Cardiovascular disease (CVD) is the leading cause of death in patients with CKD. Elevated levels of albuminuria are linked with increased risk of all-cause and cardiovascular mortality. CKD is associated with impaired quality of life and a reduced life expectancy. End-stage renal disease (ESRD) is the most severe form of CKD and is fatal if not treated with kidney replacement therapy.[2, 3, 4]

1.3. Company proposed position

The submitting company requested that empagliflozin is restricted for use in adults with CKD having individually optimised standard care (including angiotensin converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs], unless these are contraindicated or not tolerated), and either, at the start of treatment:

- an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73m^2 up to 45 mL/min/1.73m^2 or
- an eGFR of 45 mL/min/1.73m^2 up to 90 mL/min/1.73m^2 and either:
    - A urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more or
    - Type 2 Diabetes Mellitus (T2DM).

1.4. Treatment pathway and relevant comparators

The goal of treatment for CKD is to prevent kidney disease progression and to reduce cardiovascular risk. To achieve these goals, a range of interventions are utilised, including lifestyle advice, blood pressure control, lipid management, antiplatelet medicines, and glycaemic control as necessary. Renin-angiotensin system blockade with ACE inhibitors or ARBs reduce albuminuria and slow the rate of progression in proteinuric nephropathies, particularly in patients with diabetic kidney disease, and can be considered standard of care for treatment of CKD. More recently, SGLT2 inhibitors have been shown to be beneficial for patients with CKD. Dapagliflozin, an SGLT2 inhibitor, is accepted for restricted use by SMC (SMC2428) for the treatment of CKD in adults with:

- an eGFR of ≥25 to ≤75 mL/min/1.73m² at treatment initiation, and
- are receiving an ACE inhibitor or ARB (unless these are not tolerated or contraindicated), and
- have a uACR of at least 23 mg/mmol, or type 2 diabetes mellitus or both.

Finerenone (which is a non-steroidal mineralocorticoid receptor antagonist) has been accepted for use by SMC for the treatment of CKD (stage 3 and 4 with albuminuria) associated with T2DM in adults (SMC2486), however clinical experts consulted by SMC do not consider it a comparator for this submission.[2, 5, 6]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review and proposed positioning

Evidence to support the efficacy and safety of empagliflozin for the treatment of adult patients with CKD comes from EMPA-KIDNEY. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 7]

Criteria	EMPA-KIDNEY
Study design	International, randomised, double-blind, phase III study.

Eligible patients	• Age ≥ 18 years.
	• Evidence of progressive CKD at risk of kidney disease progression:
	  ○ eGFR ≥20 and <45 mL/min/1.73m² (CKD Epidemiology Collaboration formula) or:
	  ○ eGFR ≥45 and <90 mL/min/1.73m² with uACR ≥200 mg/g (22.6 mg/mmol) or protein: creatine ratio ≥300 mg/g (30 mg/mmol).
	• Treatment with a clinically appropriate dose of a single ACE inhibitor or ARB unless an investigator judged such treatments were either not indicated or would not be tolerated.

Treatments	Empagliflozin 10 mg orally once daily or placebo.
Randomisation	Patients were randomised equally. A minimised randomisation algorithm helped to ensure balance between the treatment groups with respect to the following prognostic variables: age, sex, prior diabetes, eGFR and uACR, and region.
Primary outcome	The primary outcome was the first occurrence of progression of kidney disease or death from cardiovascular causes. Progression of kidney disease was defined as the first occurrence of any of the following: • ESKD (the initiation of maintenance dialysis or receipt of a kidney transplant). • A sustained decline in eGFR to <10 mL/min/1.73m². • Death from renal causes. • A sustained decline of ≥40% in eGFR from randomisation.
Secondary outcomes	Key secondary outcomes included hospitalisation for heart failure or death from cardiovascular causes; hospitalisation for any cause; and death from any cause.
Statistical analysis	If the primary outcome was statistically significant, key secondary outcomes were formally tested using the Hochberg procedure, which controlled for multiplicity. Non-key secondary outcomes were descriptive only.

Abbreviations: ACE = angiontensin converting enzyme; ARB = angiontensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; uACR = urine albumin-creatinine-ratio.

The empagliflozin group had a statistically significant lower risk of progression of kidney disease or death from cardiovascular causes than placebo. The key secondary outcome, all cause hospitalisation, was also statistically significant. See Table 2.2 for details.

Table 2.2. Primary and key secondary outcomes of EMPA-KIDNEY (ITT population).[2]

	Empagliflozin (n= 3,304)	Placebo (n= 3,305)
Primary outcome: progression of kidney disease or death from cardiovascular causes		
Number of patients with an event	432	558
Number of events per 100 patient years	6.85	8.96
Kidney disease progression as first event	12%	15%
CV death as first event	1.5%	1.6%
Hazard ratio (95% CI)	0.72 (0.64 to 0.82) p<0.001[a]	
Key secondary outcome: hospitalisation for heart failure or death from cardiovascular causes		
Number of patients with an event	131	152
Number of events per 100 patient years	2.04	2.37
Hazard ratio (95% CI)	0.84 (0.67 to 1.07) p= 0.15	
Key secondary outcome: hospitalisation for any cause		
Number of events[b]	1,611	1,895
Number of events per 100 patient years	24.8	29.2
Hazard ratio (95% CI)	0.86 (0.78 to 0.95) p= 0.003[a]	
Key secondary outcome: death from any cause		
Number of deaths	148	167
Number of events per 100 patient years	2.28	2.58
Hazard ratio (95% CI)	0.87 (0.70 to 1.08) p= 0.21	

[a] Statistically significant result.

[b] The analysis of hospitalisations for any cause included the first and all subsequent events. 1,611 events occurred in 960 patients in the empagliflozin group, and 1,895 events occurred in 1,035 patients in the placebo group.

Abbreviations: CI = confidence intervals; CV = cardiovascular; HR = hazard ratio; ITT = intention-to-treat

2.2. Health-related quality of life outcomes

In EMPA-KIDNEY, there were no relevant treatment differences in the descriptive analyses across the treatment groups in the scores of the EQ-5D questionnaire.[2]

2.3. Supportive studies

The submitting company presented results from relevant subgroups of patients from the phase III studies EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved; EMPEROR studies were pooled. EMPA-REG OUTCOME investigated the effects of empagliflozin plus standard of care versus placebo on cardiovascular outcomes and mortality in patients with T2DM with established cardiovascular disease. The two EMPEROR studies investigated the effects of empagliflozin plus standard of care versus placebo on cardiovascular and renal outcomes in patients with chronic heart failure and reduced ejection fraction.[8, 9, 10]

The submitting company applied the following criteria to identify patients with CKD with uACR and eGFR values outside EMPA-KIDNEY criteria:

- eGFR ≥45 to <60 ml/min/1.73m^2 and uACR <200 mg/g (<22.6 mg/mmol), or
- eGFR ≥60 to <90 ml/min/1.73m^2 and uACR ≥30 to <200 mg/g (≥3.39 to <22.6mg/mmol), or
- eGFR ≥90 ml/min/1.73m^2 and uACR ≥30 mg/g (≥3.39 mg/mmol).

In both populations (EMPEROR-Pooled and EMPA-REG OUTCOME), roughly one-third of the patients had normo-albuminuria (34%), the majority of patients had microalbuminuria (63%), and only a small proportion of patients had macroalbuminuria (3.2%). All patients had an eGFR >45 mL/min/1.73 m^2. Approximately half of the EMPEROR-Pooled population were non-diabetic.[8, 9, 10, 11]

Empagliflozin reduced the risk of kidney disease progression or death from cardiovascular causes compared with placebo (EMPEROR-Pooled: HR 0.75 [95% CI 0.61 to 0.91]; EMPA-REG-OUTCOME: HR 0.44 [95% CI 0.29 to 0.65]).[8, 9, 10, 11]

A post-hoc analysis of EMPA-REG OUTCOME was also conducted among patients who would not have met renal inclusion criteria for EMPA-KIDNEY, specifically, those with eGFR ≥45 and <90 ml/min/1.73m^2 but without albuminuria (uACR < 200 mg/g [22.6mg/mmol]). In this analysis, empagliflozin reduced the risk of kidney disease progression or death from cardiovascular causes compared with placebo (HR 0.48 [95% CI 0.34 to 0.67]; p<0.001).

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing empagliflozin with relevant comparators, the submitting company presented an indirect treatment comparison versus the SGLT2 inhibitors, dapagliflozin and canagliflozin, and the non-steroidal mineralocorticoid receptor antagonist, finerenone. See Table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian NMA.
Population	Adult patients (≥18 years of age) with CKD or DKD, with or without comorbidities.
Comparators	Empagliflozin, dapagliflozin, canagliflozin and finerenone.
Studies included	13 studies included in NMA (CANVAS programme, CREDENCE, DAPA-CKD, DAPA-HF, DECLARE-TIMI 58, Dekkers 2018, MB102029, EMPA-KIDNEY, EMPA-REG OUTCOME, EMPEROR-Preserved, EMPEROR-Reduced, FIDELIO-DKD, FIGARO-DKD)
Outcomes	Efficacy outcomes included composite renal outcomes (progression of kidney disease or death from cardiovascular causes), progression to ESKD/ESRD, HHF, CV death, a composite of HHF or CV death, 3P-MACE, all-cause mortality, and ACH.
Results	There was no evidence of a difference in treatment effect for the composite renal outcome, progression of kidney disease or death from cardiovascular causes (eGFR decline ≥ 40% threshold), between empagliflozin and dapagliflozin (OR = 1.23 [95% CrI 0.71 to 2.20]). There was no evidence of a difference in treatment effect for the composite renal outcome, progression of kidney disease or death from cardiovascular causes (eGFR decline ≥ 40% threshold), between empagliflozin and finerenone (OR = 0.86 [95% CrI 0.73 to 1.02]). There was no evidence of a difference in treatment effect for the composite renal outcome, progression of kidney disease or death from cardiovascular causes (eGFR decline ≥57% threshold), between empagliflozin and canagliflozin (OR = 1.05 [95% CrI 0.79 to 1.38]).

Abbreviations: 3P-MACE = death from a cardiovascular cause, nonfatal stroke or nonfatal myocardial infarction; ACH = all-cause hospitalisations; CKD = chronic kidney disease; CrI = credible interval; CV =

cardiovascular; DKD = diabetic kidney disease; ESKD = end-stage kidney disease; ESRD = end-stage renal disease; HHF = hospitalisation for heart failure; NMA = network meta-analysis; OR = odds ratio; RCT = randomised controlled trial; SGLT2 = sodium-glucose cotransporter-2.

3. Summary of Safety Evidence

The median exposure to treatment in EMPA-KIDNEY was 22 months. Serious adverse events (SAEs) or prespecified non-serious adverse events (AEs) were reported by 44% (1,447/3,304) of patients in the empagliflozin group and 46% (1,520/3,305) in the placebo group and these were considered treatment-related in 2.4% and 1.8% respectively. In the empagliflozin and placebo groups respectively, SAEs were reported by 33% and 35%; and 7.0% and 7.3% of AEs lead to discontinuation.[2]

The most frequently reported AEs of any grade with an incidence of >2% in the empagliflozin group versus the placebo group were: gout (7.0% versus 8.0%), acute kidney injury (2.8% versus 3.5%), coronavirus infection (3.0% versus 3.2%), blood potassium increased (2.3% versus 2.6%), dehydration (2.2% versus 2.0%), and hypoglycaemia (2.1% versus 2.0%).[2]

Overall, the safety profile of empagliflozin in this setting appears reassuring and can be considered well-tolerated.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- EMPA-KIDNEY was a large, well-conducted phase III study that evaluated the efficacy and safety of empagliflozin as an addition to standard of care treatment.
- Empagliflozin demonstrated a clinically relevant, statistically significant benefit for the composite primary outcome; risk of progression of kidney disease or death from cardiovascular causes was 28% lower (HR= 0.72 [95% CI: 0.64 to 0.82]) than placebo. The primary outcome was mainly driven by an improvement in the number of patients having an eGFR reduction ≥40%, however every component of the composite outcome had a lower number of events in the empagliflozin group versus placebo.[2]
- EMPA-KIDNEY recruited a broad population of patients with CKD, with varying levels of albuminuria, eGFR, and patients with and without T2DM (46% of the study population had a history of diabetes).[2, 7]

4.2. Key uncertainties

- Patients with albuminuria may benefit more from treatment with empagliflozin. The EMPA-KIDNEY study recruited patients with normal (<3.4 mg/mmol), microalbuminura (>3.4 and <34 mg/mmol) and macroalbuminuria (>34 mg/mmol). Subgroup analyses in EMPA-KIDNEY suggested a trend toward lower efficacy with lower albuminuria, with a significant p-value for interaction (p=0.0174). In particular, patients with normal (n=1,328) and micro-albuminuria (n=1,895) had very limited or lack of treatment benefit with empagliflozin for the primary outcome, with hazard ratio (95% confidence interval [CI]) of 1.01 (0.66 to 1.55) and 0.91 (0.65 to 1.26), respectively. This contrasts with the subgroup

who had macroalbuminuria (n=3,417) and a HR (95% CI) of 0.67 (0.58 to 0.78). To support the use of empagliflozin in patients with normal and microalbuminuria, the submitting company presented subgroup analyses of the phase III studies EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved, which suggest empagliflozin was effective in patients with normal and microalbuminuria; EMPEROR-Pooled: HR 0.75 [95% CI 0.61 to 0.91]; EMPA-REG-OUTCOME: HR 0.44 [95% CI 0.29 to 0.65]). Furthermore, subgroup analyses of the secondary outcomes all-cause hospitalisation and eGFR annual slope in EMPA-KIDNEY appear to suggest efficacy across albumin levels, although these should be interpreted with caution.[1, 2]

- The number of cardiovascular events observed was low, which has implications for the statistical power and interpretation of secondary and tertiary cardiovascular outcomes.[7]
- Patients with polycystic nephropathy, patients receiving immunosuppressive medicines, and patients who had received a kidney transplant were excluded from EMPA-KIDNEY which may limit generalisability.[2]
- Approximately 58% of the study population were white, which may limit generalisability to Scottish clinical practice.[7] At 4.0% of the study population, the proportion of black patients may be underrepresented.[2]
- There is a lack of direct evidence comparing empagliflozin with the relevant comparator dapagliflozin. The ITC had limitations including: heterogeneity in baseline eGFR and uACR, which are prognostic factors; differences in the proportion of patients with history of CVD; and definition of the primary outcome. Despite these limitations it would seem reasonable to conclude that empagliflozin and dapagliflozin have similar efficacy in chronic kidney disease.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that empagliflozin in the proposed positioning would allow a greater number of patients to receive an SGLT2 inhibitor for the treatment of CKD.

4.4. Service implications

There are no anticipated service implications associated with the introduction of empagliflozin for this indication.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Kidney Research UK, which is a registered charity.
- Kidney Research UK has received 3.85% pharmaceutical company funding in the past two years, with none from the submitting company.
- Chronic kidney disease (CKD) can have a hugely negative impact on quality of life, with a range of debilitating symptoms that can impact on many aspects of life and wellbeing. Symptoms include debilitating fatigue, significant pain, itching, swelling, restless leg syndrome, muscle

cramps and sleep problems. People's capacity to stay in work, maintain relationships and quality of life can be severely compromised.

- CKD is currently incurable with limited pharmacological options for delaying progression. The uncertainty of knowing when this progression may occur also has a significant mental health burden. Treatments for kidney failure are very burdensome with limited access to transplantation. People who progress to kidney failure often find the burden of treatment is very substantial.
- The research findings that this medicine can potentially delay progression of CKD in patients offer hope. Treatments that can slow or prevent the progression of kidney disease to end stage renal failure are very likely to prove cost effective in the long-term to the health system, reducing the increase in the number of people on dialysis.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime time horizon defined as 50 years based on a starting age of approximately 63 years (mean-average age of the full cohort of patients in the EMPA-KIDNEY study).
Population	The patient population was consistent with the company's positioning as described in Section 1.3.
Comparators	The submitting company compared empagliflozin plus individually optimised standard of care (SoC) with individually optimised SoC only. A cost-minimisation analysis vs dapagliflozin in the subset of the population eligible for dapagliflozin. Both dapagliflozin and standard of care were considered relevant comparators. SoC was defined as ACE inhibitors or ARBs unless these were not tolerated or contraindicated.
Model description	A *de novo* model was developed using a Markov state patient-level microsimulation framework. The model structure was comprised of 18 mutually exclusive health states defined by Kidney Disease Improving Global Outcome (KDIGO) classification stages. Patients could transition between health states at discrete cycles and were at risk of experiencing AEs and CKD complications at any time.
Clinical data	The main source of clinical evidence used to inform the economic evaluation was the EMPA-KIDNEY study[2]. A variety of published literature sources were used to inform health outcomes for patients following discontinuation of empagliflozin.
Extrapolation	Disease progression through KDIGO health states in the treatment and comparator arms was modelled through annual treatment-specific transition probabilities derived from observed eGFR slopes and uACR changes over time in the EMPA-KIDNEY[2] study while patients are receiving treatment. Following treatment discontinuation, transition probabilities were derived from a variety of published literature sources. The discontinuation rate used for empagliflozin and placebo in the model was sourced from the EMPA-KIDNEY[2] study. The annual discontinuation rate of 12.56 and 14.16 per 100 patient years was applied while on treatment with empagliflozin and placebo respectively. The risk of all-cause mortality (ACM) was predicted using non-specific cause of death, CV death plus renal death.

Quality of life	The utility values applied in the base case were identified through a systematic literature review (SLR). A publication by Jesky 2016[12] was selected to allow utility weight inputs per health state. Utilities were assumed to be identical for the health states with the same eGFR class. The complication and adverse event disutilities were all derived from literature. Utility values in the model were not age-adjusted, however, age-adjusted utilities were provided on request with the minimal impact on the results.
Costs and resource use	Costs included in the model were medicine acquisition costs, health state costs, complication costs and adverse event costs. Measures of resources used were based on a combination of published literature studies, prior National Institute for Health and Care Excellence (NICE) Technology Appraisals (TA), and UK clinical opinion. Sources used to value resource use were NHS Reference Costs 2020/21, British National Formulary (BNF), published literature studies, and prior NICE technology appraisals.
PAS	Not applicable.

Abbreviations: ACE, angiotensin converting enzyme; AE, adverse events; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcome; SoC = standard of care; uACR = urine albumin-to-creatinine ratio;

6.2. Results

Base case economic results are presented in Table 6.2. Empagliflozin plus SoC was dominant compared to SoC only meaning it was estimated as resulting in lower costs and better health outcomes for patients.

Table 6.2. Base case results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Empagliflozin plus SoC	92,453	9.55	7.09	-6,264	0.833	Dominant -7,516
SoC	98,717	8.52	6.26	-	-	-

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life-years; QALYs = quality-adjusted life years; SoC = standard of care.
Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

Disaggregated costs showed that the largest cost savings came from fewer renal replacement therapy (RRT) inpatients in the empafliflozin + SoC arm compared to SoC due to slower disease progression to ESKD.

The company also provided a cost-minimisation analysis comparing empagliflozin with dapagliflozin in the subgroup of patients eligible to receive dapagliflozin. This analysis assumed equal efficacy based on the ITC and costs were also equal between the treatments.

6.3. Sensitivity analyses

Scenario analyses are presented in Table 6.3. A change in the eGFR threshold to 20mL/min/1.73m^2 to estimate the risk of renal replacement therapy (RRT) from 15mL/min/1.73m^2 had by far the biggest impact on the ICER with a 46% change relative to the base case result. Other scenarios with large impacts on the ICER were the use of Major et al risk equation to predict risk of RRT in place of Tangri et al and replacing acute costs with ACH. Several more scenario analyses were requested from the company and are presented in Table 6.3.

Table 6.3 Scenario analysis

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			-6,264	0.833	Dominant -7,516
1	eGFR threshold used to estimate the risk of RRT	15mL/min/1.73 m2	20mL/min/1.73 m2	-3,432	0.849	Dominant
2	Risk equation used to predict risk of RRT	Tangri et. al 2016 variable risk equation	Study by Major et al	-5,407	0.860	Dominant
3	Source for health state utility values	Literature derived	EMPA-KIDNEY study utilities	-6,264	0.920	Dominant
4	Approach to estimating costs	Included separately for CVD events, cancer, infections AKI and fractures.	Replaced with ACH cost	-5,501	0.829	Dominant
5	Patient Subgroup	No subgroup	Subgroup of patients with a uACR < 300	-501	0.970	Dominant
6	Patient Subgroup	No subgroup	Patients who have a uACR < 22	2,599	0.836	3,108
7	Patient Subgroup	No subgroup	Patients who have no diabetes and a uACR < than 22	3,201	0.826	3,874
8	Patient demographics	EMPA-KINDEY	UK Renal Report	-5,995	0.840	Dominant
9	Time Horizon (with no age-adjustment for utilities)	Lifetime	5 years	-1,957	0.090	Dominant
10	Combined scenario of scenario 6 and scenario 9			676	0.065	10,446
11	Combined scenario of scenario 7 and scenario 9			882	0.069	12,806

Abbreviations: ACH = all-cause hospitalisations; AKI = acute kidney injury; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; QALYs = quality-adjusted life years; TIA = transient ischaemic attack. Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.4. Key strengths

- The primary outcome of the EMPA-KIDNEY study was reached.
- A number of scenario analyses were provided to explore the key uncertainties.

6.5. Key uncertainties

- The company did not initially present cost-effectiveness results specifically for the empagliflozin patient population not eligible for dapagliflozin. Additional scenarios were provided to explore this uncertainty and the conclusion remained unchanged.

- The patient demographic in the model was not representative of the Scottish CKD patient population. However, a scenario analysis with a representative population was provided and the ICER remained dominant.
- Results applying utility values from the EMPA kidney are preferred. As demonstrated in scenario 3 the ICER remain dominant.

7. Conclusion

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

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published clinical guideline NG203: Chronic kidney disease: assessment and management in August 2021, which was last updated in November 2021.[5]

The UK Kidney Association (UKKA) published clinical guideline: UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transport-2 (SGLT2) Inhibition in Adults with Kidney Disease in October 2021, which was last updated April 2023.[6]

Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines were published in March 2024: CKD Evaluation and Management.[13]

9. Additional Information

9.1. Product availability date

07 September 2023.

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 01 March 2024.

10. Company Estimate of Eligible Population and Estimated Budget Impact

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.

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

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This assessment is based on data submitted by the applicant company up to and including 16 April 2024.

**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.