Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2322

dapagliflozin 10mg film-coated tablets (Forxiga®)

AstraZeneca UK Limited

05 March 2021

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 Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

dapagliflozin (Forxiga®) is accepted for use within NHSScotland.

Indication under review: in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

In a randomised, double-blind, phase III study, dapagliflozin demonstrated a significant reduction in the composite outcome of hospitalisation for heart failure, urgent heart failure visit and cardiovascular death compared with placebo in patients with heart failure with reduced ejection fraction receiving current standard of care.

Chairman
Scottish Medicines Consortium

Indication

In adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.[1]

Dosing Information

The recommended dose is 10mg dapagliflozin once daily.

Dapagliflozin can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

In the DAPA-HF study, dapagliflozin was administered in conjunction with other heart failure therapies.[1]

Product availability date

3 November 2020

Summary of evidence on comparative efficacy

Dapagliflozin is a selective and reversible sodium-glucose co-transporter 2 (SGLT2) inhibitor. Inhibition of SGLT2 causes a reduction in the reabsorption of glucose and sodium in the proximal renal tubule, which leads to urinary excretion of glucose and osmotic diuresis. An increase in the delivery of sodium to the distal tubule is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. These effects lead to a reduction in volume overload, reduce blood pressure and lower preload and afterload, which may have beneficial effects on cardiac remodelling.[1, 2]

Evidence to support the efficacy and safety of dapagliflozin for the treatment of heart failure with a reduced ejection fraction comes from DAPA-HF, an international, multicentre, randomised, double-blind, parallel group, phase III study. DAPA-HF recruited adult patients ≥18 years with a diagnosis of heart failure (NYHA functional class II to IV) which had been present for at least two months, and a documented left ventricular ejection fraction of ≤40% within the previous 12 months. Heart failure treatment was optimised and stable for at least 4 weeks before study enrolment and, unless contraindicated or not tolerated, included an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or sacubitril/valsartan and beta-blocker, and if considered appropriate by the patient's treating physician, a mineralocorticoid receptor antagonist. In addition, individual fluid/volume status was optimised with diuretic therapy. Eligible patients were required to have a plasma level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) of ≥600 picogram (pg)/mL or ≥400pg/mL if they had been hospitalised for heart failure within the previous 12 months. Patients with atrial fibrillation or flutter were required to have a NT-proBNP level of ≥900pg/mL. An estimated glomerular filtration rate (eGFR)

of ≥30mL/minute/1.73m^2 was also required. Patients with and without type 2 diabetes mellitus were eligible for this study.[2, 3]

Patients were randomised equally to receive oral dapagliflozin 10mg once daily (n=2,373) or matching placebo (n=2,371). Randomisation was stratified according to a diagnosis of type 2 diabetes mellitus (either an established diagnosis or a central laboratory glycated haemoglobin level (HbA1c) ≥6.5% [48 mmol/mol] confirmed at screening). A dose reduction of dapagliflozin to 5mg or temporary treatment discontinuation was permitted at the discretion of the investigator if an acute decline in eGFR, volume depletion or hypotension occurred, with a subsequent increase in dose or restarting treatment if clinically indicated. Unless contraindicated, patients continued to receive standard heart failure treatments. Patients with type 2 diabetes mellitus continued to take glucose-lowering treatments, doses could be adjusted to minimise the risk of hypoglycaemia.[2, 3]

The primary outcome was a composite of worsening heart failure or death from cardiovascular causes. An episode of worsening heart failure was defined as an unplanned hospital admission for heart failure or an urgent visit resulting in intravenous treatment for heart failure. Efficacy analyses were performed in the full analysis set (FAS), which comprised all randomised patients. A hierarchical statistical testing strategy was applied to the primary and secondary outcomes (which included time to first occurrence of either component of the composite of hospitalisation for heart failure or cardiovascular death; total number of first and recurrent hospitalisations for heart failure and cardiovascular death; change from baseline to month 8 in total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ); time to first occurrence of worsening renal function and death from any cause). Worsening renal function was defined as any of the components of the composite: a sustained decline in eGFR of ≥50%, end-stage renal disease (defined as a sustained [≥28 days] eGFR of <15mL/min/1.73m^2, sustained dialysis or renal transplantation) or renal death. There was no formal testing of outcomes after the first non-significant outcome in the hierarchy.[2, 3]

The study was event driven and after a median follow-up of 18.2 months (data cut-off 11 August 2019) the pre-specified stopping boundary had been met and the primary analysis was conducted. Compared with placebo, treatment with dapagliflozin resulted in a significant reduction in the composite primary outcome (absolute reduction of 4.9% and relative risk reduction of 26%). Further details including components of the primary composite outcome components, which were not formally tested for statistical significance, and secondary outcomes are presented in Table 1. Dapagliflozin did not demonstrate superiority compared with placebo for the renal composite endpoint and the hierarchical testing sequence was stopped, therefore all-cause mortality was not formally tested and considered an exploratory analysis.[2, 3]

Table 1: Primary composite and secondary outcomes from DAPA-HF in FAS

	Dapagliflozin (n=2,373)	Placebo (n=2,371)
Primary composite outcome		
Events, n(%)	386 (16%)	502 (21%)
Hazard ratio, 95% CI	0.74 (0.65 to 0.85) p<0.001	
Components of primary outcome		
Hospitalisation for heart failure, n(%)	231 (9.7%)	318 (13%)
Hazard ratio, 95% CI	0.70 (0.59 to 0.83) [A]	
Urgent heart failure visit, n(%)	10 (0.4%)	23 (1.0%)
Hazard ratio, 95% CI	0.43 (0.20 to 0.90) [A]	
Cardiovascular death, n(%)	227 (9.6%)	273 (12%)
Hazard ratio, 95% CI	0.82 (0.69 to 0.98) [A]	
Secondary outcomes		
Cardiovascular death or hospitalisation for heart failure, n (%)	382 (16%)	495 (21%)
Hazard ratio, 95% CI	0.75 (0.65 to 0.85) p<0.001	
Total number of hospitalisations for heart failure and cardiovascular death, n	567	742
Rate ratio, 95% CI	0.75 (0.65 to 0.88) p<0.001	
Change in KCCQ total symptom score at 8 months[B]	6.1	3.3
Win ratio, 95% CI	1.18 (1.11 to 1.26) p<0.001	
Worsening renal function, n (%)	28 (1.2%)	39 (1.6%)
Hazard ratio, 95% CI	0.71 (0.44 to 1.16) p=0.168	
Death from any cause, n (%)	276 (12%)	329 (14%)
Hazard ratio, 95% CI	0.83 (0.71 to 0.97) [A]	

FAS=full analysis set, CI=confidence interval, KCCQ=Kansas City Cardiomyopathy Questionnaire.

[A] not formally tested for statistical significance [B]KCCQ is a 23-item self-administered disease specific questionnaire for patients with heart failure. The total symptom score ranges from 0 to 100 with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as a win ratio with a value greater than 1 indicating superiority.

Pre-specified subgroup analyses of the primary composite outcome were generally consistent with the primary analyses. However, the magnitude of effect observed with dapagliflozin compared with placebo was less favourable in patients recruited from Europe (hazard ratio [HR] 0.84 [95% CI: 0.69 to 1.01]) and with NYHA class III to IV heart failure (HR 0.90 [95% CI: 0.74 to 1.09]). A post hoc subgroup analyses was conducted to examine the effect of background heart failure treatment (diuretic, digoxin, mineralocorticoid receptor antagonist, angiotensin receptor neprilysin inhibitor, ivabradine, implanted cardioverter defibrillating device and cardiac resynchronisation therapy) and the effect of dapagliflozin based on dose intensity (≥50% and <50% target dose) of beta-blocker, ACE inhibitor/ARB and mineralocorticoid antagonist. The benefit of dapagliflozin compared to placebo was consistent regardless of background heart failure treatment, including patients who were (HR 0.75 [95% CI: 0.50 to 1.13]) (n=508) and were not taking sacubitril/valsartan (HR 0.74 [95% CI: 0.65 to 0.86]) (n=4,236) at baseline.[3, 4]

Patient reported outcomes were assessed using the KCCQ, as a secondary outcome with results reported in Table 1. The KCCQ total symptom score quantifies heart failure symptom frequency and severity including fatigue, peripheral oedema, dyspnoea and orthopnoea. Scores range from 1 to 100 with higher scores reflecting a better health status, a ≥5 point increase in total summary score represents a clinically meaningful improvement. Compared with placebo, more patients in the dapagliflozin group had a ≥5 point increase in total summary score (58% versus 51%) and fewer in the dapagliflozin group had a ≥5 point deterioration in total summary score (25% versus 33%). Patient reported outcomes were also measured using European quality of life 5 dimensions 5 levels (EQ-5D-5L) as an exploratory outcome, results were similar in both groups at 24 months.[2]

Summary of evidence on comparative safety

Dapagliflozin has a well-established safety profile in patients with diabetes mellitus and no new safety concerns were identified in the phase III DAPA-HF study. Collection of safety data in DAPA-HF focused on serious adverse events (SAEs) and adverse events (AEs) of special interest. A SAE was reported by 36% (846/2,368) of patients in the dapagliflozin group and 40% (951/2,368) in the placebo group. In each group respectively, patients with a dose reduction due to AEs were 1.8% versus 1.1%, the proportion of AEs that led to dose interruptions were 12% versus 15% and patients discontinuing therapy due to an AE was 4.7% versus 4.9%.[2, 3]

The most frequently reported SAEs with an incidence >1% during treatment in the dapagliflozin group versus the placebo group were: cardiac failure (10% versus 14%), pneumonia (3.0% versus 3.1%), cardiac failure congestive (2.4% versus 2.7%), cardiac failure acute (1.5% versus 2.2%), death (1.4% versus 1.6%), acute myocardial infarction (1.4% versus 1.4%) and ventricular tachycardia (1.4% versus 2.2%).[2, 3]

Adverse events of special interest reported during the treatment period in the dapagliflozin group compared with the placebo group were: AEs related to volume depletion (7.2% versus 6.5%), renal events (6.0% versus 6.7%), major hypoglycaemic events (0.2% in both groups), diabetic ketoacidosis (0.1% versus 0%) and surgical amputations (0.5% in both groups). The incidence of fractures was similar between groups during the on and off treatment period however, patients with an eGFR <45mL/min/1.73m^2 had a higher incidence of fractures in the dapagliflozin group compared with the placebo group (4.1% versus 2.8%) this may have been because there were more patients with history of osteoporosis in the dapagliflozin group. During treatment, a small proportion of patients in both groups developed a urinary tract infection classed as serious or that lead to discontinuation of study treatment (0.8% and 0.9% in the dapagliflozin and placebo groups respectively). There were no confirmed cases of Fournier's gangrene. See SPC for further information. [1-3]

Summary of clinical effectiveness issues

Heart failure is a chronic disease which is caused by structural and/or functional abnormalities of cardiac function leading to reduced cardiac output or high filling pressures at rest or with stress. It may arise as a consequence of coronary artery disease, hypertension, valvular disease or myocarditis. Symptoms commonly include dyspnoea, tachycardia, night cough, fatigue, ankle oedema and pleural effusion. Scottish Intercollegiate Guidelines Network (SIGN) guidance recommends patients with NYHA class II to IV heart failure with a reduced ejection fraction, are treated with a beta-blocker and an ACE inhibitor, or an ARB if intolerant of an ACE inhibitor. A mineralocorticoid receptor antagonist should be considered for patients with a left ventricular ejection fraction ≤35% who have ongoing symptoms despite optimal treatment. Sacubitril/valsartan instead of an ACE inhibitor or ARB is recommended in patients with left ventricular ejection fraction ≤40%, NYHA class II to IV with ongoing symptoms despite optimal treatment unless contraindicated. Other treatments used less frequently include digoxin, ivabradine, hydralazine with a nitrate, cardiac resynchronisation therapy, implantable cardioverter defibrillators and surgical procedures.[5, 6] Clinical experts consulted by SMC considered that dapagliflozin fills an unmet need by providing an additional treatment option for patients with heart failure with a reduced ejection fraction.

In DAPA-HF, dapagliflozin was superior to placebo for the primary composite outcome of cardiovascular death, a heart failure hospitalisation or urgent heart failure visit (relative reduction of 26% and absolute reduction of 4.9%). The reduction was significant and the magnitude of effect was considered clinically relevant. The favourable effect was consistent across all three components of the primary composite endpoint, although this was not analysed for statistical significance, and was also supported by secondary outcomes including cardiovascular death or hospitalisation, composite outcome of cardiovascular death and recurrent heart failure hospitalisation and change from baseline at 8 months in KCCQ-TSS.[2]

Treatment with dapagliflozin did not demonstrate a significant difference in the incidence of the renal composite endpoint compared with placebo however, event rates in both groups were low. Although the favourable effects of dapagliflozin were not affected by renal function, patients with an eGFR <30mL/minute/1.73m^2 were excluded from DAPA-AF and there is limited experience in treating this patient population. The risk of all-cause mortality was lower in the dapagliflozin group compared with placebo but, following the hierarchical strategy, was not formally tested.[1-3]

A small proportion (0.9%) of the DAPA-HF study population had NYHA class IV and therefore evidence to support efficacy and safety in this subgroup is limited.[1, 2]

Patients with type 1 diabetes mellitus were excluded from DAPA-HF therefore, there is a lack of safety and efficacy data for treatment of heart failure in this population and consequently treatment of these patients is not recommended. Dapagliflozin is licensed for the treatment of adults with type 1 diabetes mellitus as an adjunct to insulin in patients with a BMI≥27kg/m^2 at the 5mg dose.[2, 3, 7]

In DAPA-HF, patients had a mean age of 66 years, this is generally younger than those seen in clinical practice (mean age at diagnosis is 77 years[8]). Patients were also excluded if they had a systolic blood pressure of <95mmHg. These factors may affect generalisability to Scottish clinical practice.

Patients in DAPA-HF were required to have a diagnosis of heart failure for at least 2 months and stabilised on optimised heart failure treatment for at least 4 weeks before study enrolment.[3] Therefore the treatment effect in patients who are not yet stabilised on standard heart failure treatment or are newly diagnosed remains unclear.

A post hoc subgroup analysis of the primary composite outcome indicated the favourable effects of dapagliflozin were demonstrated regardless of background heart failure therapy including patients receiving sacubitril/valsartan at baseline. However, this subgroup was relatively small (n=508) and DAPA-HF was not powered to detect differences between subgroups therefore the results should be treated with caution.[2]

The effect of dapagliflozin compared with placebo for the primary composite endpoint was less favourable in the subgroups of patients with NYHA class III or IV and those patients recruited from Europe. In both subgroups this was because of a lack of effect on the cardiovascular death component of the primary composite endpoint. However, there was no credible explanation to this variation in treatment effect and favourable effects were demonstrated for the reduction of hospitalisations for heart failure in the NYHA class III and IV subgroup which is a clinically relevant outcome, therefore a benefit of treatment is expected in patients with more severe heart failure. In the European study population, there was a higher representation of patients who had factors associated with numerically lower efficacy including more severe NYHA class and presence of atrial fibrillation and ischaemia.[2, 3]

Clinical experts consulted by SMC considered dapagliflozin is a therapeutic advancement when added to standard treatment in patients with heart failure with a reduced ejection fraction due to improvements in morbidity and mortality demonstrated in the DAPA-HF study. They consider it will provide an additional treatment option for patients already established on optimised therapy who remain symptomatic. Dapagliflozin is a once daily dose that does not require titration, which may be advantageous for some patients.

Summary of comparative health economic evidence

The submitting company originally provided a cost-minimisation analysis (CMA) as its base-case assessing dapagliflozin for the treatment of heart failure with reduced ejection fraction according to the licensed indication. This compared dapagliflozin versus sacubitril/valsartan following initial treatment with first-line therapies, however, clinical experts suggested that dapagliflozin will be used as an add-on therapy and is, therefore, not expected to displace any medications making a CMA inappropriate for decision making. The company provided an additional comparison of dapagliflozin versus placebo as add-on treatment to mixed background therapy. Mixed background therapy was defined as the combinations of treatments used at baseline as optimum

therapy in the DAPA-HF study that included: ACE inhibitor/ARB, beta blocker, sacubitril/valsartan, ivabradine, hydralazine, digoxin and device therapy. This additional comparison was felt to provide a more relevant basis for decision-making, and is the focus of the rest of the DAD.

A *de novo* economic model was created in the form of a Markov state-transition cohort model, stratified by type 2 diabetes mellitus (T2DM) status, covering a total of 9 health states. Health states were primarily defined according to patients Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) and were categorised into quartiles (0 - < 58, 58 - < 77, 77 - < 92 and 92 -100). Patients could transition to the absorbing state of death at any time. A one month cycle length was used with a lifetime time horizon and an NHSScotland and social work perspective was utilised. The discount rate used in the analysis was 3.5% p.a. for costs and benefits as appropriate.

Clinical effectiveness data were obtained from the phase 3 randomised DAPA-HF study[3], which informed patient characteristics, KCCQ-TSS quartile health state transition probabilities, time-variant transition probabilities for mortality, incidence of hospitalisation for heart failure (hHF) and urgent heart failure visit (uHFv), incidence of adverse events (AEs) and incidence of treatment discontinuation. Cardiovascular (CV) and all-cause mortality were estimated by fitting a series of parametric curves to data from the DAPA-HF study whilst adjusting for statistically significant co-variables. Non-CV mortality was estimated by the difference in CV and all-cause mortality predicted by the parametric curves fitted to this data. Based on clinical expert opinion and a comparison of life expectancy estimates against those from previously published health technology assessments, the company selected the Weilbull parametric curve to extrapolate survival beyond the study follow-up period. The incidence of hHF and uHFv events were estimated via a similar process to mortality with generalised estimating equations fitted to the study data under an assumption that events are Poisson-distributed. The treatment effect of dapagliflozin in terms of improvement in survival and reduction in hospitalisations was assumed to continue for the duration of the model and patients were assumed to discontinue treatment at a rate of 7% per annum.

The majority of utility values were estimated from a pooled analysis of individual patient data from the DAPA-HF study; EQ-5D-5L data were collected at multiple points during the trial, which were subsequently cross-walked to EQ-5D-3L scores using an algorithm developed by van Hout et al[9]. Following adjustment for key covariates (e.g. sex, KCCQ TSS quartile, T2DM), utility values were estimated for health states (range: 0.600 – 0.833) and disutilities estimated for specific adverse events.

Medicine acquisition costs for dapagliflozin were included in the analysis as well as costs for background therapies however it is unclear if the cost of antidiabetic medications due to T2DM were included. The dose and duration of dapagliflozin was assumed to be 10mg once daily and no administration costs were included for dapagliflozin on the basis that it is an oral therapy. Resource use associated with the management of HF was measured by reference to a study by McMurray et al[10] while resource use associated with T2DM was taken from a publication by Alva et al[11]. AE costs were also included and patients who discontinued treatment with dapagliflozin

due to tolerability were assumed to incur costs estimated from the placebo arm of the DAPA-HF study.

The economic results for dapagliflozin versus placebo as an add-on treatment to mixed background therapy are shown in Table 2 and show that over a lifetime time horizon dapagliflozin is associated with incremental costs of £2,870 and quality-adjusted life-years (QALYs) of 0.475 versus placebo, resulting in an incremental cost-effectiveness ratio (ICER) of £6,048 per QALY.

Table 2: Economic results: NDC-preferred base-case

Description	Incremental costs	Incremental QALYs	ICER (£/QALY)
Dapagliflozin versus placebo, as add-on therapies to mixed background therapy	£2,870	0.475	£6,048

Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

Disaggregated analyses indicate that incremental costs associated with dapagliflozin are primarily costs from purchase of the medicine itself with a smaller proportion due to larger background medical management costs following an increase to life expectancy. This is partially offset by reductions in costs associated with hospitalisation for HF and CV-specific mortality. Similarly, the majority of incremental QALYs associated with dapagliflozin consist of a larger proportion of patient time being spent in health states with higher quality of life combined with an increase in life expectancy.

Key scenario analyses shown in Table 3 indicate that overall the cost-effectiveness of dapagliflozin is relatively stable but has moderate upward sensitivity to use of a different cut-off point for calculating transition probabilities between health states, a more conservative approach to extrapolating mortality data and use of alternative health state utility values.

Table 3: Key scenario analyses: NDC-preferred base-case

#	Scenario	Alternative assumption or value	Δ costs	Δ QALYs	ICER (£/QALY)
-	NDC-preferred base-case		£2,870	0.475	£6,048
1	Time horizon	5 years	£1,413	0.140	£10,102
2		10 years	£2,268	0.319	£7,103
3		15 years	£2,670	0.419	£6,364
4	Health state transitions	Transition probability matrices based on data from months 0-8 and month 9 onwards of the DAPA-HF trial	£2,688	0.379	£7,084
5	CV and all-cause mortality extrapolation	Gompertz	£1,894	0.253	£7,488
6		Log-logistic	£3,061	0.501	£6,111
7		Lognormal	£3,444	0.577	£5,971
8	T2DM at baseline	Baseline characteristics: T2DM subgroup, 100% T2DM	£2,921	0.445	£6,571

#	Scenario	Alternative assumption or value	Δ costs	Δ QALYs	ICER (£/QALY)
9		Baseline characteristics: No T2DM subgroup, 0% T2DM	£2,803	0.496	£5,648
10	Age at baseline	Baseline characteristics: Age >65 subgroup	£2,622	0.428	£6,131
11	Alternative health state utility values	Alternative health state utility values based on Sullivan et al. 2011	£2,870	0.441	£6,513
12	Combined scenario analyses	Scenarios: 4, 5 and 11	£1,822	0.194	£9,413
13		Scenarios: 4, 7 and 11	£3,399	0.469	£7,242

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; CV, cardiovascular; hHF, hospitalisation for heart failure; MRA, mineralocorticoid receptor antagonist; T2DM, type 2 diabetes mellitus.

The following limitations are noted regarding the economic evaluation:

- The model structure does not allow the probability of future cardiovascular events to be dependent on patient history. The use of a model type that could account for patient history may improve the cost-effectiveness of dapagliflozin, as prior heart failure hospitalisation is associated with worse future outcomes.
- The cut-off point used to calculate transition probabilities for movements between KCCQ-TSS quartiles (4 months post randomisation) appears too short and may over-estimate the relative effectiveness of dapagliflozin. However, further analyses provided by the company (scenario 4) using a later cut-off point (8 months) suggest that this does not have a significant impact on the results.
- The number of patients who received specific combinations of therapies as background therapy is small for some combinations and therefore the company's conclusion that the treatment effect of dapagliflozin does not vary by baseline therapy may be premature.
- The cost of antidiabetic medicines has not been included in the analysis but further analyses provided by the company suggest the inclusion of these costs does not have a large impact on results.

Despite these issues, the economic case was considered demonstrated.

Summary of patient and carer involvement

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

- We received a patient group submission from Pumping Marvellous Foundation, which is a registered charity.
- Pumping Marvellous Foundation has received 68.5% pharmaceutical company funding in the past two years, including from the submitting company.

- Heart failure is a chronic condition with substantial impacts on quality of life. Common symptoms include breathlessness, fatigue and oedema. Amongst other issues, heart failure can also cause muscular pain and cramps, chest pain and difficulty sleeping and concentrating. The emotional impact can also be hugely detrimental and may add to the care burden of the condition.

- Current treatments can cause issues with blood pressure, renal function or potassium levels. Also, despite the optimisation of current treatments, some people who live with heart failure are still symptomatic suffering from breathlessness, oedema and chronic fatigue.

- Dapagliflozin would be another treatment option for those who remain symptomatic despite optimisation of current treatment. It may be beneficial in that it can have a lesser impact on blood pressure and does not require titration or specialist prescribing. People who have used dapagliflozin report positive impacts on their energy and breathlessness levels. People with heart failure welcome the possibility of a new treatment that could lower the risk of early death and improve quality of life.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Management of chronic heart failure (SIGN 147) in March 2016 and the guideline was revalidated in 2019.[5] The guideline makes the following relevant recommendations:

- All patients with heart failure with reduced ejection fraction, NYHA class II-IV, should be started on beta blocker therapy as soon as their condition is stable.

- Patients with heart failure with reduced ejection fraction of all NYHA functional classes, should be given angiotensin-converting enzyme inhibitors.

- Patients with heart failure with reduced ejection fraction, NYHA class II-IV, who are intolerant of angiotensin-converting enzyme inhibitors should be given an angiotensin receptor blocker.

- An angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor should be considered in patients with heart failure with reduced ejection fraction NYHA class II-IV, who are unable to tolerate a mineralocorticoid receptor antagonist.

- Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-IV, LVEF ≤35%, despite optimal treatment, should be given mineralocorticoid receptor antagonist unless contraindicated by the presence of renal impairment (chronic kidney disease stage ≥4–5) and/or elevated serum potassium concentration (K+ >5.0 mmol/L).

- Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-III, LVEF ≤40% despite optimal treatment should be given

sacubitril/valsartan instead of their ACE inhibitor or ARB, unless contraindicated. It may be considered in patients with NYHA class IV symptoms.

If the patient is already on an ACE inhibitor, the ACE inhibitor should be stopped for 36 hours before initiating sacubitril/valsartan to minimise the risk of angioedema.

- Patients with a diagnosis of heart failure with reduced ejection fraction of NYHA class II-IV, LVEF ≤35%, who have had a previous hospital admission for heart failure in the preceding 12 months but have stabilised on standard therapy for at least four weeks should be given ivabradine. Patients must have a sinus rhythm heart rate ≥75 beats/minute despite maximum tolerated dose of beta blockers.
- Patients with heart failure and clinical signs or symptoms of fluid overload or congestion should be considered for diuretic therapy.
- Digoxin should be considered as an add-on therapy for patients with heart failure in sinus rhythm who are still symptomatic after optimum therapy.
- NT-proBNP-guided treatment may be considered in patients with heart failure aged less than 75 years, especially in the presence of higher baseline NT-proBNP levels (>2,114 pg/mL).

A treatment algorithm for patients with heart failure with reduced ejection fraction (HFrEF) is included as Figure 2 of the SIGN guideline.[5]

European Society of Cardiology (ESC) published Guidelines for the diagnosis and treatment of acute and chronic heart failure in 2016.[12] This guidance makes a number of relevant recommendations based on available evidence:

- An ACE inhibitor (or ARB if ACE-inhibitor is not tolerated) is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalisation and death.
- A beta-blocker is recommended, in addition an ACE-inhibitor (or ARB if ACE inhibitor is not tolerated) for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalisation and death.
- A MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-inhibitor (or ARB if ACE-inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalisation and death.

The ESC guidance includes a treatment algorithm for the use of these treatments based on a number of clinical parameters. The guidance also recommends:

- Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.
- Diuretics should be considered to reduce the risk of HF hospitalisation in patients with signs and/or symptoms of congestion.
- Sacubitril/valsartan is recommended as a replacement for an ACE-inhibitor to further

reduce the risk of HF hospitalisation and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-inhibitor, a beta-blocker and an MRA.

- Ivabradine should be considered to reduce the risk of HF hospitalisation or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of betablocker (or maximum tolerated dose below that), ACE-inhibitor (or ARB), and an MRA (or ARB).
- Ivabradine should be considered to reduce the risk of HF hospitalisation and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-inhibitor (or ARB) and an MRA (or ARB).
- An ARB is recommended to reduce the risk of HF hospitalisation and cardiovascular death in symptomatic patients unable to tolerate an ACE-inhibitor (patients should also receive a beta-blocker and an MRA).
- An ARB may be considered to reduce the risk of HF hospitalisation and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.
- Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-inhibitor a beta-blocker and an MRA to reduce the risk of HF hospitalisation and death.
- Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-inhibitor nor an ARB (or they are contra-indicated) to reduce the risk of death.
- Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-inhibitor (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalisation (both all-cause and HF-hospitalisations).
- An n-3 PUFA preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalisation and cardiovascular death.[12]

Additional information: comparators

The submitting company consider the main use of dapagliflozin will be as an alternative to sacubitril/valsartan however, clinical experts consulted by SMC considered it would provide an additional treatment option for patients already optimised on standard treatment who remain symptomatic.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Dapagliflozin	10mg once daily	476

Costs from BNF online [07/12/2020].

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 24,701 patients eligible for treatment with dapagliflozin in year 1 rising to 35,187 patients in year 5. Experts consulted by SMC estimated that there would be fewer patients eligible for treatment with dapagliflozin in Scotland.

Based on an estimated uptake of 2.20% in year 1 (543 patients) and 24.90% in year 5 (8,762 patients), the impact on the medicines budget was estimated at £241k in year 1 rising to £3.9m in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is equivalent to the gross impact.

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This assessment is based on data submitted by the applicant company up to and including 12 February 2021.

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.