

Empagliflozin for treating chronic heart failure with reduced ejection fraction

Technology appraisal guidance

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www.nice.org.uk/guidance/ta773

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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This guidance should be read in conjunction with QS9.

1 Recommendations

- 1.1 Empagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimised standard care with:
 - an angiotensin-converting enzyme (ACE) inhibitor or angiotensin 2 receptor blocker (ARB), with a beta blocker and, if tolerated, a mineralocorticoid receptor antagonist (MRA), or
 - sacubitril valsartan with a beta blocker and, if tolerated, an MRA.
- 1.2 Start empagliflozin for treating symptomatic heart failure with reduced ejection fraction on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.
- 1.3 This recommendation is not intended to affect treatment with empagliflozin that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with heart failure with reduced ejection fraction may have symptoms that are not controlled well enough despite being on the most appropriate (optimised) standard care. Standard care includes an ACE inhibitor or an ARB, with a beta blocker and, if tolerated, an MRA. Then, if symptoms continue on this, people may be offered sacubitril valsartan with a beta blocker and, if tolerated, an MRA.

Evidence from a clinical trial shows that empagliflozin plus standard care reduces the risk of dying from cardiovascular causes compared with placebo plus standard care. It also shows that it reduces the likelihood of hospitalisation for heart failure. There are no trials directly comparing empagliflozin with the most appropriate comparator, dapagliflozin.

However, an indirect comparison suggests that empagliflozin is likely to be similar to dapagliflozin in reducing the risk of dying and the likelihood of hospitalisations for heart failure.

The cost-effectiveness estimates for empagliflozin are within what NICE normally considers an acceptable use of NHS resources. So empagliflozin is recommended.

Increased monitoring or changes to other medicines being taken may be needed for treating heart failure with empagliflozin. So, it should only be started on advice from a heart failure specialist.

2 Information about empagliflozin

Marketing authorisation indication

- 2.1 Empagliflozin (Jardiance, Boehringer Ingelheim) has a marketing authorisation 'in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price of 10 mg or 25 mg empagliflozin is £36.59 per 28-tablet pack (excluding VAT; BNF online, accessed November 2021). The annual treatment cost is £476.98. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Boehringer Ingelheim, a review of this submission by the evidence review group (ERG) and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The condition

People with chronic heart failure with reduced ejection fraction would welcome a new treatment option

- 3.1 Heart failure with reduced ejection fraction is a chronic condition that affects survival and quality of life. The patient experts highlighted the psychological effects of a diagnosis. They explained that breathlessness, extreme fatigue and fluid accumulation in particular can be debilitating. Clinical expert submissions to NICE confirmed that heart failure with reduced ejection fraction is associated with high rates of death and hospitalisation. They also stated that there is an unmet need for new treatment options. Current treatments aim to manage symptoms and stabilise the disease to prevent further decline in quality of life and to keep people alive longer. The clinical experts explained that, despite optimising therapies, many people still have symptoms, including breathlessness. The patient experts said that they would welcome a new treatment option, especially if it could be used early in the treatment pathway. The committee concluded that there is an unmet need for a new treatment option for symptomatic chronic heart failure with reduced ejection fraction. It also concluded that people with the condition and healthcare professionals would welcome a new treatment option.

The treatment pathway

People should be optimised on standard care before having a sodium-glucose co-transporter 2 (SGLT2) inhibitor

3.2 [NICE's guideline on diagnosing and managing chronic heart failure in adults](#) recommends a range of drug treatments for newly diagnosed heart failure with reduced ejection fraction. These are separated into first-line and specialist treatments. First-line treatments include angiotensin-converting enzyme (ACE) inhibitors, or angiotensin 2 receptor blockers (ARBs) when an ACE inhibitor is not tolerated. Beta blockers can also be offered and a mineralocorticoid receptor antagonist (MRA) can be offered if appropriate and tolerated. The company's submission had suggested that empagliflozin should be positioned as an add-on to first-line treatment in people with heart failure with reduced ejection fraction who may or may not have comorbidities. The committee understood that this is narrower than the marketing authorisation, which does not specify use as an add-on treatment for heart failure with reduced ejection fraction. The clinical experts said the company's positioning was now in line with the [European Society of Cardiology guidelines on the diagnosis and treatment of acute and chronic heart failure](#). These guidelines recommend that empagliflozin or dapagliflozin (another SGLT2 inhibitor) could be started earlier in the care pathway for heart failure with reduced ejection fraction. The committee noted this was not directly in line with [NICE's technology appraisal guidance on dapagliflozin for treating chronic heart failure with reduced ejection fraction](#). This recommends that dapagliflozin is used after standard care is optimised. The committee noted that there are a range of treatments for heart failure with reduced ejection fraction. It concluded that empagliflozin was an appropriate treatment that should be used as an add-on to optimised standard care.

Dapagliflozin is the most appropriate comparator for this appraisal

3.3 The final scope for this appraisal listed 2 comparators: individually optimised standard care without empagliflozin, and dapagliflozin as an

add-on to standard care. The company stated that individually optimised standard care was the most relevant comparator. That is, people should have the most appropriate treatments used for standard care before starting treatment with empagliflozin. This was because most people with heart failure with reduced ejection fraction in England and Wales would have at least one of these treatment options. It did not consider dapagliflozin to be a relevant comparator because it considered that this was not standard care in the NHS. It cited recent market data suggesting that dapagliflozin is used by very few people with heart failure alone, and is most frequently used by people with heart failure and type 2 diabetes. The committee noted that [NICE's technology appraisal guidance on dapagliflozin for treating chronic heart failure with reduced ejection fraction](#) had only been published in February 2021 so there had been a relatively short period of time to consider uptake. The clinical experts stated uptake had increased widely since publication of the guidance and that it would now be considered as standard care. The committee considered whether empagliflozin and dapagliflozin would likely be used interchangeably in the same place in the treatment pathway for chronic heart failure with reduced ejection fraction. The clinical experts said that the [European Society of Cardiology guidelines on the diagnosis and treatment of acute and chronic heart failure](#) did not distinguish between the 2 SGLT2 inhibitors. For this reason, they would also consider that empagliflozin and dapagliflozin would be used in the same groups of people. They further noted that it would be unlikely that someone who is not eligible for treatment with dapagliflozin would be eligible for treatment with empagliflozin. This was because the technologies are considered to work in the same way. The committee concluded that dapagliflozin was the most appropriate comparator for this appraisal.

Clinical evidence

EMPEROR-Reduced is the key trial and is broadly generalisable to NHS clinical practice

- 3.4 EMPEROR-Reduced was a double-blind randomised clinical trial comparing empagliflozin plus standard care with placebo plus standard care. Standard care could include medical therapy with an ACE inhibitor,

an ARB, a beta blocker or an MRA. The trial included people aged at least 18 who had had a diagnosis of chronic heart failure for at least 3 months. They had moderate to severe heart failure with reduced ejection fraction. This was defined by a left ventricular ejection fraction of 40% or less based on the New York Heart Association functional class 2 to 4. The clinical experts said that the trial findings were generalisable to NHS clinical practice. However, they highlighted several differences between the population in EMPEROR-Reduced and people having treatment in the NHS:

- The average age in the intention-to-treat population was 67 years, while the average in the NHS at diagnosis is 77 years.
- The proportion of women (24%) was smaller than would be expected in the NHS.
- The proportion of people using an ACE inhibitor or ARB was lower than would be expected in the NHS.

The ERG stated that the characteristics of people in EMPEROR-Reduced, may not reflect that of the population in the NHS. The clinical experts agreed this might be an issue of how people are recruited to take part in clinical trials. People who are older and who might have more comorbidities would be less likely to be involved in a clinical trial so they might be under-represented. The committee noted EMPEROR-Reduced was not powered to show any difference in subgroups by age. The clinical experts said there would be no apparent reason why relative treatment effects would be different between subgroups of younger and older ages. The committee concluded that data from the intention-to-treat population in EMPEROR-Reduced was broadly generalisable to NHS clinical practice.

Empagliflozin plus standard care compared with placebo plus standard care is clinically effective

- 3.5 The primary efficacy outcome in EMPEROR-Reduced was a composite of cardiovascular death and hospitalisation for heart failure. Intention-to-treat analyses showed that empagliflozin plus standard care reduced the incidence of the primary outcome by 25.0% compared with placebo plus standard care (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.65

to 0.86; $p < 0.0001$). At a median follow up of 16 months, results showed that 19.4% of people having empagliflozin plus standard care had an event compared with 24.7% in the placebo group. The committee concluded that empagliflozin is clinically effective compared with placebo and that it reduces the risk of cardiovascular events when added to standard care.

Indirect treatment comparison

The indirect treatment comparison shows that clinical outcomes between empagliflozin and dapagliflozin are similar

3.6 There were no trials directly comparing empagliflozin with dapagliflozin so the company presented an indirect treatment comparison using the Bucher method. This compared the results from EMPEROR-Reduced with those from DAPA-HF. DAPA-HF was a phase 3 multinational double-blind randomised controlled trial. It compared dapagliflozin plus standard care with placebo plus standard care in people with stable symptoms of heart failure with reduced ejection fraction. The company supported the indirect comparison with the results from a published pooled meta-analysis reported by Zannad et al. (2020). This pooled data for dapagliflozin and empagliflozin to create class effect estimates for SGLT2 inhibitors compared with placebo. The ERG broadly agreed that the results from the meta-analyses suggested there was a statistically significant benefit with SGLT2 inhibitors compared with placebo for all outcomes. However, the ERG noted that the results of the meta-analysis were only based on 1 trial of empagliflozin and 1 trial of dapagliflozin. It therefore considered the Bucher comparison was a more appropriate method of assessing the comparative efficacy of empagliflozin compared with dapagliflozin. The results of the indirect treatment comparison suggested there was no difference between empagliflozin and dapagliflozin in any of the outcomes (all results are confidential and cannot be reported here). However, the results suggested a trend towards possible differences in cardiovascular deaths, all-cause mortality and renal function. The committee was aware that the ERG had explored this uncertainty in the cost-utility analysis (see [section 3.8](#)). The committee noted that there were some baseline differences in the

Bucher indirect treatment comparison between people in EMPEROR-Reduced and DAPA-HF. People in EMPEROR-Reduced may have had a more severe renal impairment than people in DAPA-HF. This meant that people in EMPEROR-Reduced may have been more likely to have a hospitalisation for heart failure or mortality event compared with those in DAPA-HF. The committee acknowledged the limitations of the comparison but agreed it was appropriate for decision making. The committee concluded that the results of the Bucher indirect treatment comparison showed that the clinical outcomes between empagliflozin and dapagliflozin are similar.

The company's economic model

The company's model is suitable for decision making

3.7 The company modelled cost effectiveness using a state transition model with 5 states (4 based on symptom severity plus 1 for death). It captured disease severity using the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS). This is a disease-specific measure of quality of life. People transitioned through quartiles based on KCCQ-CSS (0 to 100, with high scores indicating lower symptom burden), and a specific utility and cost associated with each state. The committee considered whether the KCCQ is an appropriate measure to capture quality-of-life outcomes. It noted that there may be some inconsistencies in how the size of effect translates from trial data to modelled quality-of-life effects. The clinical experts explained that the KCCQ is a well-validated comprehensive quality-of-life and symptom questionnaire for heart failure. The ERG stated that it was satisfied with the company's choice of KCCQ-CSS states in the model. The committee concluded that the company's model structure was appropriate for decision making.

Cost-effectiveness estimates

Empagliflozin is recommended as an option for treating chronic heart failure with reduced ejection fraction

3.8 The company considered that a cost-comparison was the most appropriate way to estimate the cost effectiveness of empagliflozin compared with dapagliflozin. This was based on an assumption of equivalent effectiveness between empagliflozin and dapagliflozin. It noted that both drugs had the same list price, dosing frequency and method of administration, and that available evidence suggested the treatments were clinically equivalent. The ERG suggested that a cost-utility analysis may have been more appropriate. This was because the company's assumption of equal effectiveness was based on only 2 trials and ignored potential uncertainty (see [section 3.6](#)). After technical engagement, the company provided a cost-utility analysis to help with decision making. However, it argued that this type of analysis would amplify any uncertainty in the results of the indirect treatment comparison. The company's base-case cost-utility analysis assumed there was no survival benefit with empagliflozin over dapagliflozin. However, it assumed that taking empagliflozin would lead to improvements in renal function and reduced hospitalisations for heart failure. This was based on the results of the Bucher indirect treatment comparison (see [section 3.6](#)). The company's probabilistic and deterministic cost-effectiveness estimates suggested that empagliflozin dominated dapagliflozin (meaning it was less costly and at least equally effective). The ERG did additional scenario analyses to show the effect of adding the different outcomes included in the Bucher indirect treatment comparison. These scenarios included the following assumptions:

- equal effectiveness in all outcomes
- survival benefit for dapagliflozin
- survival benefit for dapagliflozin and a reduction in hospitalisations for heart failure for empagliflozin
- survival benefit for dapagliflozin, a reduction in hospitalisations for heart failure

and an improvement in renal function for empagliflozin.

For the assumption of equal effectiveness, the results showed no difference in total costs or quality-adjusted life years between the 2 treatments. The results for the other scenarios included in the ERG's analyses were in the south-west quadrant of the cost-effectiveness plane. This means that empagliflozin was estimated to be less costly and less effective than dapagliflozin (the exact results are academic in confidence and cannot be reported here). The committee understood that the ERG's scenarios were exploratory only. It also agreed that they were uncertain. This was because they were based on the results of the Bucher indirect treatment comparison, which showed no overall difference between the 2 treatments. The committee considered its earlier conclusion that dapagliflozin was the most appropriate comparator (see [section 3.3](#)) based on:

- its comparable mechanism of action
- its use in a comparable place in the treatment pathway
- the results of the indirect treatment comparison, which showed no difference between the 2 treatments.

The committee was satisfied that empagliflozin is similarly effective to dapagliflozin and that its costs are identical. It concluded to recommend empagliflozin as an option for treating symptomatic chronic heart failure with reduced ejection fraction.

Empagliflozin is not a step-change in treatment but does provide choice for people with heart failure with reduced ejection fraction

- 3.9 The committee recalled that people with heart failure with reduced ejection fraction have a poor prognosis and that there is an unmet need for treatment options (see [section 3.1](#)). It noted that empagliflozin is not the first drug of its class to gain regulatory approval for use in heart failure. So, it could not be considered a step-change in treatment. However, the committee concluded that it could be considered a relevant addition to current treatments and increase clinical choice.

Other factors

No equalities considerations were identified

- 3.10 The committee noted that the meta-analysis by Zannad et al. (2020; see [section 3.6](#)) suggested that SGLT2 inhibitors were most effective in people with a black or Asian family background. It noted that EMPEROR-Reduced mainly included people with a white family background. The committee noted that neither EMPEROR-Reduced or DAPA-HF was powered to show difference between subgroups of different ages or people from a different family background. The clinical experts said that there is no reason to restrict empagliflozin use in adults based on age or family background. The committee noted that its recommendations applied to all people regardless of family background. It recognised that there were no ongoing clinical trials or data collection to validate the possibility of differences in treatment effect because of family background. But it considered that there may be the potential to explore this issue further in future research.

A heart failure specialist should advise on starting empagliflozin and the most appropriate healthcare professional should monitor treatment

- 3.11 [NICE's guideline on chronic heart failure in adults: diagnosis and management](#) recommends that a specialist heart failure multidisciplinary team should work in collaboration with the primary care team to start new medicines that need specialist supervision. The committee noted that people taking empagliflozin for heart failure who also have diabetes might need adjustments in their diabetes medication for safety reasons because of an increased risk of ketoacidosis. The committee considered that risk factors should be identified, and some increased monitoring may be needed for treating heart failure with empagliflozin. So, it considered that a heart failure specialist was the most appropriate clinician to advise on starting treatment. The committee also noted that the summary of product characteristics states an assessment of renal function is recommended before starting empagliflozin and this should be done periodically during treatment. So, the committee considered that

monitoring should be done by the most appropriate healthcare professional. The committee further noted that NICE's technology appraisal guidance on dapagliflozin for treating chronic heart failure with reduced ejection fraction included recommendations on who should advise on starting treatment and appropriate monitoring. The committee concluded that a heart failure specialist should advise on starting empagliflozin and monitoring should be done by the most appropriate healthcare professional.

4 Implementation

- 4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has heart failure with reduced ejection fraction and the doctor responsible for their care thinks that empagliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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