

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Proposed Health Technology Appraisal

### Dapagliflozin for treating heart failure with reduced ejection fraction

#### Draft scope (pre-referral)

#### Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of dapagliflozin within its marketing authorisation for treating adults with chronic heart failure with reduced ejection fraction.

#### Background

Heart failure is a complex clinical syndrome of signs and symptoms, generally defined as the inability of the heart to supply sufficient blood flow to meet the body's needs. It is caused by structural or functional abnormalities of the heart, commonly resulting from coronary artery disease. Heart failure may be associated with left ventricular systolic dysfunction (that is, reduced left ventricular ejection fraction, where the left pumping chamber's ability to pump is impaired) but may also be associated with preserved ejection fraction (minimum ejection fraction of 45%).

Symptoms of heart failure commonly include breathlessness, fatigue and ankle swelling. Quality of life is affected by the physical limitations imposed by the symptoms.

Nearly 500,000 people in England have heart failure.<sup>1</sup> There were 188,683 hospital admissions in England for heart failure in 2018/19.<sup>2</sup> 67% of people with heart failure had a reduced left ventricular ejection fraction.<sup>3</sup> Both the prevalence and incidence of heart failure increase with age. Thirty to forty percent of people diagnosed with heart failure die within the first year.

[NICE guideline 106 for chronic heart failure in adults](#) recommends offering an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker for people with heart failure with reduced ejection fraction. If ACE inhibitors are contraindicated or not tolerated, an angiotensin receptor blocker (ARB) should be considered. A mineralocorticoid receptor antagonist (MRA) in addition to an ACE inhibitor (or ARB) and beta-blocker should be offered if symptoms continue. If neither ACE inhibitors or ARBs are tolerated, specialist advice should be sought and treatment with hydralazine in combination with nitrate can be considered.

For people who remain symptomatic on standard of care NICE [technology appraisal guidance 388](#) recommends sacubitril valsartan only in people:

- with New York Heart Association (NYHA) class II to IV symptoms and
- with a left ventricular ejection fraction of 35% or less and

- who are already taking a stable dose of ACE inhibitors or ARBs

When beta-blocker therapy is contraindicated or not tolerated NICE [technology appraisal guidance 267](#) recommends ivabradine in combination with standard therapy for people:

- with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and
- who are in sinus rhythm with a heart rate of 75 beats per minute or more and
- with a left ventricular ejection fraction of 35% or less.

### The technology

Dapagliflozin (Forxiga, AstraZenaca) is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor. SGLT-2 inhibitors prevent the kidneys from reabsorbing glucose into the blood, with excess glucose removed in the urine. This increases the total volume of urine and removes more interstitial fluid from the body. It is administered orally.

Dapagliflozin does not currently have a marketing authorisation in the UK for chronic heart failure with reduced ejection fraction. It has been studied in combination with standard care in 3 randomised controlled trials compared with placebo, in adults with an established documented diagnosis of symptomatic heart failure with reduced ejection fraction (NYHA functional class II-IV) for at least 2 months, who had a left ventricular ejection fraction of 40% or less.

<b>Intervention(s)</b>	Dapagliflozin in combination with standard care (including treatment with a beta blocker and an aldosterone antagonist).
<b>Population(s)</b>	Adults with chronic heart failure with reduced ejection fraction.
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• ACE inhibitor in combination with standard care.</li> </ul> <p>For people in whom an ACE inhibitor is unsuitable:</p> <ul style="list-style-type: none"> <li>• Angiotensin II receptor blocker in combination with standard care.</li> <li>• Mineralocorticoid receptor antagonist (MRA) in addition to an ACE inhibitor (or ARB) and beta-blocker.</li> </ul> <p>For people in whom ACE inhibitors and ARBs are unsuitable:</p> <ul style="list-style-type: none"> <li>• Hydralazine in combination with nitrate.</li> </ul>

	<ul style="list-style-type: none"> <li>• Ivabradine in combination with standard therapy.</li> </ul> <p>For people in whom beta-blocker therapy is contraindicated or not tolerated:</p> <ul style="list-style-type: none"> <li>• Sacubitril valsartan in combination with standard therapy.</li> </ul> <p>Standard care includes treatment with a beta blocker and an aldosterone antagonist.</p>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• symptoms of heart failure</li> <li>• hospitalisation for heart failure</li> <li>• all-cause hospitalisation</li> <li>• mortality</li> <li>• cardiovascular mortality</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p> <p>The cost of background therapies, such as diuretics for people with oedema, should also be included in cost effectiveness analyses.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p>Related Technology Appraisals:</p> <p><a href="#">Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction</a> (2016) NICE</p>

	<p>technology appraisal 388</p> <p><a href="#">Ivabradine for treating chronic heart failure</a> (2012) NICE technology appraisal guidance 267</p> <p>Related Guidelines:</p> <p><a href="#">Chronic heart failure in adults: diagnosis and management</a> (2018) NICE guideline NG106</p> <p>Related Quality Standards:</p> <p><a href="#">Chronic heart failure in adults</a> (2011) NICE quality standard 9</p> <p>Related NICE Pathways:</p> <p><a href="#">Chronic heart failure</a> (2019) NICE pathway</p>
<p><b>Related National Policy</b></p>	<p>The NHS Long Term Plan, 2019. <a href="#">NHS Long Term Plan</a></p> <p>NHS England (2018/2019) <a href="#">NHS manual for prescribed specialist services (2018/2019)</a></p> <p>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2. <a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a></p>

### Questions for consultation

Have all relevant comparators for dapagliflozin been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for chronic heart failure with reduced ejection fraction?  
Is standard care defined appropriately?

Are the outcomes listed appropriate?

The key trial for dapagliflozin included people with left ventricular ejection fraction of 40% or less, are outcomes likely to vary according to left ventricular ejection fraction?  
If so would this limit who is likely to receive dapagliflozin in practice?

Are there any subgroups of people in whom dapagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider dapagliflozin will fit into the existing NICE pathway, Chronic heart failure?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which dapagliflozin will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider dapagliflozin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of dapagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

NICE has published an addendum to its guide to the methods of technology appraisal (available at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf>), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

## References

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1. British Heart Foundation. Heart statistics, BHF statistics fact sheet England. Accessed September 2019. Available at: <https://www.bhf.org.uk/what-we-do/our-research/heart-statistics>

Draft scope for the proposed appraisal of Dapagliflozin for treating heart failure with reduced ejection fraction. Issue Date: November 2019

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2. NHS Digital (2019) Hospital admitted patient care activity, 2018-19: Primary diagnosis 3 character. Accessed September 2019. Available at: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19>
  3. National Institute for Cardiovascular Outcomes Research (2018) National heart failure audit 2016/17. Accessed September 2019. Available at: <https://www.nicor.org.uk/wp-content/uploads/2018/11/Heart-Failure-Summary-Report-2016-17.pdf>