NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Empagliflozin for treating chronic heart failure with reduced ejection fraction

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of empagliflozin within its marketing authorisation for treating 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. Other conditions that can increase the risk of heart failure include; ischemic heart disease, atrial fibrillation, valve disease, hypertension, diabetes, chronic obstructive pulmonary disease, and asthma. 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 reduced ejection fraction, defined as an ejection fraction below 40% in NICE guideline 106 for chronic heart failure in adults.

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

More than 550,000 people in England have heart failure[1]. There were 94,185 hospitalisations in England for heart failure in 2019/20[2]. 66% of people with heart failure have a reduced left ventricular ejection fraction[3]. Both the prevalence and incidence of heart failure increase with age. 30 to 40% of people diagnosed with heart failure die within the first year, with a 5-year mortality rate of about 50%.

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. If symptoms worsen or become severe despite first-line treatment, specialist advice should be sought and treatment with digoxin can be considered.

NICE technology appraisal guidance 388 recommends sacubitril valsartan as an option for treating symptomatic chronic heart failure with reduced ejection fraction, 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

Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE's guideline on chronic heart failure in adults: diagnosis and management.

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
- who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and
- with a left ventricular ejection fraction of 35% or less

Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers, and aldosterone antagonists. Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

The technology

Empagliflozin (Jardiance, Boehringer Ingelheim) is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor. The mechanism of action of empagliflozin in heart failure with reduced ejection fraction is not yet fully understood.It is administered orally.

Empagliflozin does not currently have a marketing authorisation in the UK for chronic heart failure with reduced ejection fraction. It is being studied in randomised controlled trials compared with placebo, in adults with an diagnosis of chronic heart (NYHA functional class II-IV) failure with left reduced ejection fraction of 40% or less.

Intervention(s)	Empagliflozin in combination with standard care (including diuretics, treatment with an ACE inhibitor, ARBs, mineralocorticoid receptor antagonist, beta blockers and cardiac devices)
Population(s)	Adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction

Comparators	Individually optimised standard care without empagliflozin. Standard care is defined as: • ACE inhibitors in combination with beta-blockers, and/or mineralocorticoid receptor antagonists • ARBs in combination with beta-blockers, and/or mineralocorticoid receptor antagonists • Sacubitril valsartan in combination with beta-blockers, and/or mineralocorticoid receptor antagonists Digoxin Ivabradine Hydralazine in combination with nitrate Dapagliflozin as an add on to standard care (subject to ongoing NICE appraisal)
Outcomes	The outcome measures to be considered include: • symptoms of heart failure • hospitalisation for heart failure • all-cause hospitalisation • mortality • cardiovascular mortality • kidney function • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The cost of background therapies, such as diuretics for people with oedema, should also be included in cost effectiveness analyses.
Other considerations	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.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (2016) NICE technology appraisal 388 Ivabradine for treating chronic heart failure (2012) NICE technology appraisal guidance 267 Related Guidelines: Chronic heart failure in adults: diagnosis and management (2018) NICE guideline NG106 Related Quality Standards: Chronic heart failure in adults (2011) NICE quality standard 9 Related NICE Pathways: Chronic heart failure (2019) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)

	Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1,2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

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

Which treatments are considered to be established clinical practice in the NHS for heart failure with reduced ejection fraction?

Would people who are eligible for empagliflozin already be on an optimised treatment regime?

How should standard care be defined?

Are the outcomes listed appropriate?

The key trial for empagliflozin 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 empagliflozin in practice?

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

Where do you consider empagliflozin 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 empagliflozin 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 empagliflozin 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 empagliflozin 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

1. British Heart Foundation. Heart statistics, BHF statistics fact sheet England. Accessed November 2020. Available at: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics
2. NHS Digital (2020) Hospital admitted patient care activity, 2019-20: Primary diagnosis 3 character. Accessed November 2020. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20
3. National Institute for Cardiovascular Outcomes Research (2019) National heart failure audit 2017/18. Accessed November 2020. Available at: https://www.hqip.org.uk/wp-content/uploads/2019/09/Ref-129-Cardiac-Heart-Failure-Summary-Report-2019-FINAL.pdf