National Institute for Health and Care Excellence

Health Technology Evaluation

Dapagliflozin for treating heart failure with preserved or mildly reduced ejection fraction

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	Yes, this topic is appropriate for a NICE appraisal.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
	The Pumping Marvellous Foundation	It is appropriate	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Yes. Heart Failure preserved Ejection Fraction (HFpEF) is a growing problem with an ageing population. The are no specific therapies to manage and treat this condition.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.

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Wording	AstraZeneca	The appropriate patient population for this appraisal is adults with symptomatic chronic heart failure (HF) with left ventricular ejection fraction (LVEF) ≥40% (HF with preserved ejection fraction [HFpEF] >50% or HF with mildly reduced ejection fraction [HFmrEF] 40-50%). This is aligned to the population investigated in the DELIVER trial which is the pivotal study for dapagliflozin in this indication. It is therefore expected that the DELIVER trial will provide clinical data on the efficacy of dapagliflozin in patients with HF with LVEF ≥40%, and as such, the expected, license indication will be for [redacted] The wording of the remit should reflect the full population to be appraised.	Thank you for your comment. The remit has been updated to specify that the population is symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more.
	The Pumping Marvellous Foundation	Wording reflects the issue	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Yes [the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology that NICE should consider].	Thank you for your comment. No action required.
Timing Issues	AstraZeneca	To date, there has been no effective, NICE-recommended therapies for the treatment of people with heart failure with an LVEF ≥40%. As a result, current treatment options are limited, with treatment often focussed on symptomatic control and/or palliative care. Therefore, patients with HFpEF or HFmrEF face significant disease morbidity and high mortality, with around 24% patients dying within the first year of diagnosis, and a 5-year mortality rate of approximately 55%. As such, there is an urgent and critical need for NICE to appraise dapagliflozin within its anticipated marketing authorisation to provide a long-awaited, effective and targeted treatment for this disease.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.

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		The submission timelines for this appraisal are well aligned to our anticipated regulatory timelines.	
	The Pumping Marvellous Foundation	Very important considering this is a first in class treatment in HFpEF. Highly innovative	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
	UK Clinical Pharmacy Association (UKCPA)	HFpEF as a heart failure diagnosis is becoming more frequent. Any new treatments that will benefit patients either in terms of symptoms or prognosis will be beneficial.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
Additional comments on the draft remit	AstraZeneca	NA	Thank you for your response. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	AstraZeneca suggests the following additions/amendments to the background information presented within the draft scope: • HF is not always due to thickening of the heart muscle so we suggest removing this and replacing it with the clear definitions of HFpEF and HFmrEF provided in the new ESC guideline for the diagnosis and management of acute and chronic heart failure. These state that there is a	Thank you for your comment. The background section of the scope has been amended to reflect these comments.

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		substantial overlap of clinical characteristics, risk factors, patterns of cardiac remodelling, and outcomes among the LVEF categories in HF. They detail that patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF, in that they are more commonly men, younger, and are more likely to have CAD and less likely to have AF and non-cardiac comorbidities.[1] • According to the ESC guideline, those with HFpEF are more often older and female than those with HFmrEF and HFrEF, and AF, CKD, and non-CV comorbidities are more common in patients with HFpEF than in those with HFrEF. There are numerous potential causes of HFpEF.[1] Regarding the therapies recommended in NICE guideline 106, calcium channel blockers, amiodarone and anticoagulants are not commonly used in clinical practice and are not considered standard of care for individuals with HF with LVEF ≥40%. We therefore suggest that reference to these are removed from the remit and scope.	
	The Pumping Marvellous Foundation	Accurate	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	'Heart failure may be associated with impaired filling of the left ventricle when the heart muscle is thickened, often as a result of long-standing high blood pressure. This is called heart failure with preserved ejection fraction.[1] The European Society of Cardiology suggests that a left ventricular ejection fraction of 50% or more should be used to define preserved ejection fraction.[6'] The above statement could be better worded. Heart failure is often categorised as HF reduced EF with and EF <40% or HFpEF >50% (as per ESC guidance).	Thank you for your comment. The background section of the scope has been amended. The 2020/21 QOF was published in September 2021 and is the most recent QOF available, where the prevalence of heart failure in the UK is

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		The most recent estimate for UK prevelance of Heart failure is 920,000 with 60,000 new cases annually. NICE guideline [NG106] The following statement should be removed as incorrect - 'The guideline also recommends calcium-channel blockers, amiodarone (in consultation with a specialist) and anticoagulants to treat all types of heart failure.'	550,613. This data source is more recent than NICE guideline 106, which was published in 2018. The statement that NICE guideline 106 recommends calcium-channel blockers, amiodarone and anticoagulants to treat all types of heart failure has been removed.
The technology/ intervention	AstraZeneca	AstraZeneca requests that the following information is included with respect to the pivotal trial, DELIVER, in the Technology section: • Dapagliflozin is being studied in the DELIVER trial, a randomised, double-blind, placebo-controlled study in patients with HFpEF and HFmrEF (symptomatic heart failure [NYHA class II-IV] with a left ventricular ejection fraction ≥40% and evidence of structural heart disease), evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background standard of care therapy, including treatments to control co-morbidities, in reducing the composite of cardiovascular death or heart failure events. **Intervention section** • AstraZeneca requests that the description of the intervention is updated to "Dapagliflozin (10 mg daily) in combination with standard care"	Thank you for your comment. The description in the scope is only intended to provide a brief overview of the technology and clinical trial. No change has been made to the technology section. The intervention section does not include information on dosing. No change needed. The description of standard care has been

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		• Due to the lack of targeted, efficacious, or NICE-approved therapies for the treatment of adults with HF with LVEF ≥40%, there is no recognised standard care. As such, treatment is typically focused on symptom control and palliative care. • Whilst there is no widely recognised standard care, dapagliflozin is anticipated to be used alongside therapies used for symptom control such a loop diuretics and management of any underlying comorbidities. Therefore, the most appropriate comparator is placebo. The scope states that standard care includes calcium channel blockers, amiodarone and anticoagulants. As stated above, these are not part of routine clinical practice in people with HF with EF ≥40% and AstraZeneca requests that these are removed from all definitions of standard care.	updated to remove calcium channel blockers, amiodarone and anticoagulants.
	The Pumping Marvellous Foundation	Accurate description	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	There is no mention that this agent was originally design as a antidiabetic agent and has been on the market for a number of year before being utilised for heart failure. Standard of care for the treatment of HFpEF currently is only diuretics and not calcium-channel blockers, amiodarone and anticoagulants	Thank you for your comment. The scope is intended to provide a brief description of the technology. No change needed. The intervention and comparators sections of the scope have been updated to remove calcium channel

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			blockers, amiodarone and anticoagulants.
Population	AstraZeneca	The appropriate patient population for this appraisal is adults with symptomatic chronic HF with LVEF ≥40% (HFpEF >50% or HFmrEF 40-50%). This is aligned to the population investigated in the DELIVER trial which is the pivotal study for dapagliflozin in this indication, as well as with the expected license indication: [redacted] It is critical that both of these populations are clearly named within the scope since they are considered as separate subgroups clinically and based on the evidence from the DELIVER trial the anticipated MHRA license will cover all chronic HF, including HFrEF (LVEF<40%), HFmrEF and HFpEF.	Thank you for your comment. The population has been updated to adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more.
	The Pumping Marvellous Foundation	It is the whole population.	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Needs clearly defining in terms of EF. Either as per clinical trial or Esc definition.	Thank you for your comment. The population has been updated to adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more.
Comparators	AstraZeneca	As discussed above, calcium channel blockers, amiodarone and anticoagulants are not typically used in UK clinical practice to treat HFpEF or mrEF. There are currently no disease modifying treatment options for this	Thank you for your comment. The

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		patient population and the only appropriate comparator is placebo plus standard care without dapagliflozin which may consists of loop diuretics prescribed for symptom relief plus any additional therapies used to treat comorbidities which will vary between patient.	comparators section of the scope has been amended to reflect this.
	The Pumping Marvellous Foundation	Agree with comparators	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	The only comparator would be diuretics.	Thank you for your comment. The comparators section of the scope has been updated.
Outcomes	AstraZeneca	The outcomes listed are appropriate and represent those most clinically relevant to HFpEF and HFmrEF.	Thank you for your comment. No action required.
	The Pumping Marvellous Foundation	Agree – however we should be measuring QOL as a whole not just the domains that are measured using health questionnaires	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Yes [these outcome measures capture the most important health related benefits (and harms) of the technology].	Thank you for your comment. No action required.

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Economic analysis	AstraZeneca	AstraZeneca has no comments relating to the economic analysis for this appraisal. An economic model is being constructed in Microsoft Excel to estimate the cost-effectiveness of dapagliflozin vs standard care from a UK NHS and personal social services perspective. The cost-effectiveness of treatments will be expressed in terms of cost per quality adjusted life year (QALY) and a lifetime time horizon will be adopted in order to capture all relevant differences in costs and outcomes between the technologies being compared.	Thank you for your comment. No action required.
	The Pumping Marvellous Foundation	Agreed	Thank you for your comment. No action required.
Equality	AstraZeneca	**Appraisal population** It is critical that the population covered in this appraisal is amended to include those with HFmrEF as well as those with HFpEF to ensure that all HF patients with a LVEF of ≥40% who currently have no disease modifying treatment options are not denied access to an effective therapy that is anticipated to be licensed for all patients with chronic HF. **Use of dapagliflozin in primary care** Dapagliflozin is currently available across primary and secondary care treatment settings for patients with T2DM, HFrEF and soon to be chronic kidney disease (CKD; TAG to be published 09/03/22).[2] A positive recommendation for dapagliflozin in HFpEF and mrEF (i.e. an LVEF ≥40%) is expected to extend the benefits of dapagliflozin to all eligible patients with HF.	Thank you for your comment. This has been reflected in the background section and population section of the updated scope. Differences in the prevalence cannot be addressed in a technology appraisal.

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		AstraZeneca understands that the majority of patients with HFpEF or mrEF are managed in the primary care setting and in many areas there are no specialist led clinics organised or funded to manage these patients. Enabling initiation of dapagliflozin for the treatment of people with HFpEF and HFmrEF would ensure consistent equality of access without relying on specialist care, which may not exist in many areas for these patients.	The committee will consider whether its recommendations could have a detrimental impact on people protected by the equality legislation. The committee may also take into account other socio-economic factors using NICE's manual and principles.
	The Pumping Marvellous Foundation	Agreed	Thank you for your comment. No action required.
Other considerations	The Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.
	The Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.
Innovation	AstraZeneca	People with HF with LVEF ≥40% currently have no NICE approved disease modifying treatment options and despite the severity of the disease standard care aims only to relieve symptoms. As highlighted in the Background section	Thank you for your comment. The committee will consider

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		of the draft scope, approximately a quarter of those diagnosed will die within a year, rising to over half by year 5.[1] These mortality rates are higher than those for many forms of cancer including breast, cervical, prostate, multiple myeloma, non-Hodgkin lymphoma, Hodgkin's disease and similar to many other types of cancer.[3] The introduction of dapagliflozin will represent a step-change in the treatment of patients with HF with a LVEF ≥40%.	the innovation of the technology during the evaluation. No action required.
	The Pumping Marvellous Foundation	This is highly innovative, first in class for the whole treatment population. It is important we consider this when making market access decisions.	Thank you for your comment. The committee will consider the innovation of the technology during the evaluation. No action required.
Questions for consultation	AstraZeneca	Comments have been provided above with regards to the population, comparators and outcomes specified in the draft scope, as well as issues related to equality, and the innovation that dapagliflozin is expected to offer patients and the health system. Answers to additional questions have been provided below: **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?**	Thank you for your comments. No action required.

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		AstraZeneca is not currently aware of any patient subgroups within the submission population of adults with HF with a LVEF ≥40% in which dapagliflozin is expected to be more clinically effective or cost-effective. **Where do you consider dapagliflozin will fit into the existing NICE pathway, Chronic heart failure?** In addition to the existing placement of dapagliflozin within the 'Treating heart failure with reduced ejection fraction' part of the Managing chronic heart failure pathway, in line with this appraisal dapagliflozin would also be added to the 'Treating heart failure with preserved ejection fraction' section. Here, dapagliflozin 10 mg would be recommended as the first line therapy for all patients diagnosed with HF with a LVEF >40%, alongside loop diuretics for symptom relief. **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?** The use of dapagliflozin as a treatment for patients with HF with LVEF ≥40% is likely to offer significant benefits from a carer perspective given the severely debilitating nature of the disease and the lack of targeted, effective treatment options. Whilst the model doesn't consider wider societal and carer benefits, these should be considered by the committee. In addition, HF with a LVEF ≥40% is associated with significant morbidity and high rates of mortality, with 24% patients dying within the first year of diagnosis, and more than 55% dying within 5 years. AstraZeneca believes	

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		that given the lack of innovative or targeted treatments for this severely debilitating condition, with standard care focused on symptom control and palliative care, dapagliflozin is likely to qualify for a severity modifier in this indication. **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.** Oral dapagliflozin has been widely used in the NHS, in both primary and secondary care settings, as a treatment for T2DM and HFrEF since the recommendations by NICE in 2013 and 2020 respectively.[4, 5] As such, both primary and secondary care clinicians have extensive clinical experience in prescribing dapagliflozin. However, given the current lack of specialists HF services that treat HF patients with a LVEF≥40%, the role of primary care in initiating treatment with dapagliflozin in this population becomes even more critical to ensure that this lack of commissioned specialist services doesn't become a barrier to adoption.	
	The Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	Subgroups where Dapagliflozin may be more effective: consider EF <60%	Thank you for your comment. The committee will consider whether there are any

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			appropriate subgroups as part of the appraisal.
Any additional comments on the draft scope	AstraZeneca	No further comments.	Thank you for your comment. No action required.
	The Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.
	UK Clinical Pharmacy Association (UKCPA)	The clinical trial for Dapagliflozin in HFpEF is not currently available. It is difficult to comment on health related benefits.	Thank you for your comment. No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope